Safeguarding the Bioeconomy (2020)

DETAILS

392 pages | 6 x 9 | PAPERBACK
ISBN 978-0-309-49567-7 | DOI 10.17226/25525

CONTRIBUTORS

Committee on Safeguarding the Bioeconomy: Finding Strategies for Understanding, Evaluating, and Protecting the Bioeconomy While Sustaining Innovation and Growth; Board on Life Sciences; Board on Agriculture and Natural Resources; Board on Science, Technology, and Economic Policy; Board on Health Sciences Policy; Forum on Cyber Resilience; Division on Earth and Life Studies; Policy and Global Affairs; Health and Medicine Division; Division on Engineering and Physical Sciences; National Academies of Sciences, Engineering, and Medicine

SUGGESTED CITATION

National Academies of Sciences, Engineering, and Medicine 2020. *Safeguarding the Bioeconomy*. Washington, DC: The National Academies Press. https://doi.org/10.17226/25525.

SAFEGUARDING the BIOECONOMY

Committee on Safeguarding the Bioeconomy:
Finding Strategies for Understanding, Evaluating, and Protecting
the Bioeconomy While Sustaining Innovation and Growth

Board on Life Sciences

Board on Agriculture and Natural Resources

Division on Earth and Life Studies

Board on Science, Technology, and Economic Policy

Policy and Global Affairs

Board on Health Sciences Policy

Health and Medicine Division

Forum on Cyber Resilience

Division on Engineering and Physical Sciences

A Consensus Study Report of

The National Academies of
SCIENCES • ENGINEERING • MEDICINE

THE NATIONAL ACADEMIES PRESS
Washington, DC
www.nap.edu

THE NATIONAL ACADEMIES PRESS 500 Fifth Street, NW Washington, DC 20001

This activity was supported by the Office of the Director of National Intelligence under Award Number WC133R17CQ0031. Any opinions, findings, conclusions, or recommendations expressed in this publication do not necessarily reflect the views of any organization or agency that provided support for the project.

International Standard Book Number-13: 978-0-309-49567-7
International Standard Book Number-10: 0-309-49567-9
Digital Object Identifier: https://doi.org/10.17226/25525
Library of Congress Control Number: 2020930894

Additional copies of this report are available from the National Academies Press, 500 Fifth Street, NW, Keck 360, Washington, DC 20001; (800) 624-6242 or (202) 334-3313; http://www.nap.edu.

Printed in the United States of America

Suggested citation: National Academies of Sciences, Engineering, and Medicine. 2020. *Safeguarding the Bioeconomy.* Washington, DC: The National Academies Press. https://doi.org/10.17226/25525.

The National Academies of
SCIENCES • ENGINEERING • MEDICINE

The **National Academy of Sciences** was established in 1863 by an Act of Congress, signed by President Lincoln, as a private, nongovernmental institution to advise the nation on issues related to science and technology. Members are elected by their peers for outstanding contributions to research. Dr. Marcia McNutt is president.

The **National Academy of Engineering** was established in 1964 under the charter of the National Academy of Sciences to bring the practices of engineering to advising the nation. Members are elected by their peers for extraordinary contributions to engineering. Dr. John L. Anderson is president.

The **National Academy of Medicine** (formerly the Institute of Medicine) was established in 1970 under the charter of the National Academy of Sciences to advise the nation on medical and health issues. Members are elected by their peers for distinguished contributions to medicine and health. Dr. Victor J. Dzau is president.

The three Academies work together as the **National Academies of Sciences, Engineering, and Medicine** to provide independent, objective analysis and advice to the nation and conduct other activities to solve complex problems and inform public policy decisions. The Academies also encourage education and research, recognize outstanding contributions to knowledge, and increase public understanding in matters of science, engineering, and medicine.

Learn more about the National Academies of Sciences, Engineering, and Medicine at **www.nationalacademies.org.**

The National Academies of
SCIENCES • ENGINEERING • MEDICINE

Consensus Study Reports published by the National Academies of Sciences, Engineering, and Medicine document the evidence-based consensus on the study's statement of task by an authoring committee of experts. Reports typically include findings, conclusions, and recommendations based on information gathered by the committee and the committee's deliberations. Each report has been subjected to a rigorous and independent peer-review process and it represents the position of the National Academies on the statement of task.

Proceedings published by the National Academies of Sciences, Engineering, and Medicine chronicle the presentations and discussions at a workshop, symposium, or other event convened by the National Academies. The statements and opinions contained in proceedings are those of the participants and are not endorsed by other participants, the planning committee, or the National Academies.

For information about other products and activities of the National Academies, please visit www.nationalacademies.org/about/whatwedo.

COMMITTEE ON SAFEGUARDING THE BIOECONOMY: FINDING STRATEGIES FOR UNDERSTANDING, EVALUATING, AND PROTECTING THE BIOECONOMY WHILE SUSTAINING INNOVATION AND GROWTH

THOMAS M. CONNELLY, JR., *Chair*, American Chemical Society, Washington, DC
STEVEN M. BELLOVIN, Columbia University, New York, New York
PATRICK M. BOYLE, Ginkgo Bioworks Inc., Boston, Massachusetts
KATHERINE CHARLET, Carnegie Endowment for International Peace, Washington, DC
CAROL CORRADO, The Conference Board, New York, New York
J. BRADLEY DICKERSON, Sandia National Laboratories, Albuquerque, New Mexico
DIANE DIEULIIS, National Defense University, Washington, DC
GERALD EPSTEIN, National Defense University, Washington, DC
STEVEN L. EVANS, Dow Agro Science (retired), Indianapolis, Indiana
GEORGE B. FRISVOLD, University of Arizona, Tucson
JEFFREY L. FURMAN, Boston University, Boston, Massachusetts
LINDA KAHL, SciScript Communications, Walnut Creek, California
ISAAC S. KOHANE, Harvard Medical School, Boston, Massachusetts
KELVIN H. LEE, University of Delaware, Newark
MARY E. MAXON, Lawrence Berkeley National Laboratory, Berkeley, California
MAUREEN McCANN, Purdue University, West Lafayette, Indiana
PIERS D. MILLETT, iGEM, Boston, Massachusetts

Staff

ANDREA HODGSON, Study Director, Board on Life Sciences
FRANCES SHARPLES, Board Director, Board on Life Sciences
KATHERINE BOWMAN, Senior Program Officer, Board on Life Sciences
STEVEN M. MOSS, Associate Program Officer, Board on Life Sciences
KOSSANA YOUNG, Senior Program Assistant, Board on Life Sciences
KARA LANEY, Senior Program Officer, Board on Agriculture and Natural Resources
GAIL COHEN, Board Director, Board on Science, Technology, and Economic Policy
STEVEN KENDALL, Program Officer, Board on Science, Technology, and Economic Policy

SCOTT WOLLEK, Senior Program Officer, Board on Health Sciences Policy
LYNETTE MILLETT, Director, Forum on Cyber Resilience

Consultants

RONA BRIERE, Editor
ALISA DECATUR, Editorial Assistant

Acknowledgments

This Consensus Study Report was greatly enhanced by discussions with participants at the committee's meetings and workshops as part of this study (a full list of participants is available in Appendix B). The committee would particularly like to acknowledge the efforts of those who contributed to its information-gathering efforts through personal discussions, informal requests for information, or some other mechanism: Laura Haas, University of Massachusetts Amherst; Tony Sager, Center for Internet Security; and Fred Schneider, Cornell University.

This Consensus Study Report was reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise. The purpose of this independent review is to provide candid and critical comments that will assist the National Academies of Sciences, Engineering, and Medicine in making each published report as sound as possible and to ensure that it meets the institutional standards for quality, objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process.

The committee thanks the following individuals for their review of this report:

PATRICIA BRENNAN, National Library of Medicine
JOHN CUMBERS, SynBioBeta
DREW ENDY, Stanford University
RICHARD B. FREEMAN, Harvard University

MICHELLE GARFINKEL, EMBO
VAL GIDDINGS, Information Technology and Innovation Foundation
ANDY HINES, University of Houston
JOSEPH KANABROCKI, The University of Chicago
STEVEN B. LIPNER, SAFECode
BEN PETRO, U.S. Department of Defense
GENE ROBINSON, University of Illinois at Urbana-Champaign
HOWARD B. ROSEN, Independent Consultant
PHILIP P. SHAPIRA, University of Manchester
DARLENE SOLOMON, Agilent
SAMUEL S. VISNER, MITRE Corporation
DAVID ZILBERMAN, University of California, Berkeley

Although the reviewers listed above provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations of this report, nor did they see the final draft before its release. The review of this report was overseen by **MICHAEL R. LADISCH,** Purdue University, and **PETER CARR,** Massachusetts Institute of Technology. They were responsible for making certain that an independent examination of this report was carried out in accordance with the standards of the National Academies and that all review comments were carefully considered. Responsibility for the final content rests entirely with the authoring committee and the National Academies.

Preface

The U.S. bioeconomy comprises exciting science- and technology-driven economic activity that is expanding and advancing on many fronts. Americans' everyday lives benefit from the U.S. bioeconomy in terms of the food they eat; the health care they receive; the quality of their environment; and the fuels, materials, and products they consume, and the bioeconomy is poised to make even larger contributions in all of these sectors and possibly some additional areas as well. U.S. science and technology are the source of all of these benefits. Fueled by public and private investment, the nation has maintained a considerable technological lead in the bioeconomy domain, and for an extended period of time.

At the same time, the powerful technologies encompassed by the bioeconomy can also lead to national security and economic vulnerabilities. For example, biotechnology can be misused to create virulent pathogens that can target our food supply (crops and animals) or even the human population. Engineering biology can be used to eliminate invasive species, yet such actions can have unintended environmental consequences. Genomic technology can be used to design disease therapies that are tailored to an individual, yet this same technology can be used to identify genetic vulnerabilities in a population or subpopulation. Large genetic databases allow people's ancestry to be revealed and crimes to be solved, but such data can also be misused. And while genetic and other large datasets contribute to medical progress, they also represent potential security and privacy concerns.

During the past decade, moreover, competition in the global bioeconomy has intensified. Although economic competition has always been part of global commerce, global competition has in some respects moved beyond the usual economic rivalry among nations. Outright theft of intellectual property and know-how has occurred in some cases. Cross-border cyber intrusion has led to exfiltration of proprietary information and data from U.S. organizations by individuals and entities in other countries. More subtle loss of competitiveness can also occur. As a result of some countries' policies, an asymmetry exists in the way information is shared, whereby the ability of U.S.-based researchers to access and use such information is denied. While one response is retaliation with similar policies, this response would be counter to the system that gave rise to the global bioeconomy and the broader scientific enterprise. The entire world has benefited from the exchange of scientific information built on collaborative efforts of scientists around the world.

These security and economic concerns provided the impetus for the study documented in this report, which was requested by the Office of the Director of National Intelligence. To carry out the study, the National Academies of Sciences, Engineering, and Medicine convened the Committee on Safeguarding the Bioeconomy: Finding Strategies for Understanding, Evaluating, and Protecting the Bioeconomy While Sustaining Innovation and Growth. Convened in December 2018, the 17-member committee was charged with investigating strategies for understanding, evaluating, and protecting the bioeconomy while sustaining innovation and growth. Given the breadth of this task, the committee's membership represents a broad range of expertise, including life sciences, engineering, computer science, economics, law, strategic planning, and national security. The committee members have current or past experience in academia, federal agencies, national laboratories, nongovernmental organizations, and industry (large and entrepreneurial companies), and have worked in many bioeconomy sectors, including human health, pharmaceuticals, agriculture, and industrial bioscience.

The committee met four times in face-to-face meetings between January and June 2019. Three of these meetings included open workshop sessions. An additional three webinars were held to which the public was also invited. During these meetings and webinars, the committee heard from a total of 36 speakers (see Appendix B) on every facet of the U.S. bioeconomy. In addition, the committee members met privately in numerous conference calls, both as a full committee and in small groups.

The work of this committee was ably assisted by the essential support of the staff of the National Academies. Given the breadth of our task, significant contributions were made by staff from the Board on Life Sciences; the Board on Agriculture and Natural Resources; the Board

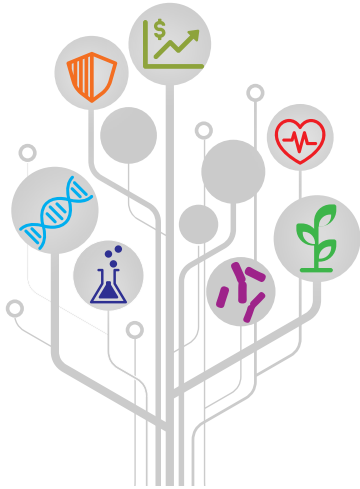
on Science, Technology, and Economic Policy; the Board on Health Sciences Policy; and the Forum on Cyber Resilience. This study could not have been completed without their outstanding efforts. The committee especially wishes to acknowledge the guidance and leadership of study director Andrea Hodgson.

The committee's task was daunting in scope. As noted above, it was charged with developing strategies for understanding and evaluating the U.S. bioeconomy, as well as recommending strategies for protecting the bioeconomy while sustaining innovation and growth. Central to our work were the somewhat opposed notions of safeguarding and growth, of security and openness. Science and innovation thrive when ideas, information, products, services, and data are freely exchanged. The United States has an open and welcoming culture. As a nation, it is open by intent and by preference, and it has benefited enormously from this openness. In all aspects of the committee's deliberations, as it strove for consensus in its recommendations, the need to address security concerns while preserving the benefits of openness was a primary consideration. The committee recognizes that international collaborations are essential to the continued success of the U.S. bioeconomy.

While the choices are not always easy, prudent decisions can be made. The committee does believe in the nation's ability both to safeguard the bioeconomy and to further its growth. In our view, the recommendations presented in this report can serve as important steps toward fully realizing the promise and potential of the U.S. bioeconomy.

Thomas M. Connelly, Jr., *Chair*
Committee on Safeguarding the Bioeconomy: Finding Strategies for Understanding, Evaluating, and Protecting the Bioeconomy While Sustaining Innovation and Growth

Contents



SUMMARY[1]

Over the past 50 years, the integration of engineering principles and advances in computing and information sciences has transformed the life sciences and biotechnology. The ability to read genetic code, edit an organism's genome, and create organisms with entirely synthetic genomes are just a few of the breakthroughs that have changed the way research is done and the types of products that can be created. The economic activity related to the life sciences research enterprise is referred to conceptually as the bioeconomy. Examples of bioeconomy products include chemicals made though biosynthetic pathways rather than solely chemical synthesis (such as 1,3-propanediol), microorganisms that act as environmental biosensors, fabrics made from biosynthetic spider silk, and novel foods and food additives made from yeast or bacteria. The U.S. bioeconomy provides a means of developing new and innovative products and achieving such benefits as lower carbon consumption and improved health care solutions. It also has opened new avenues for innovation, job creation, and economic growth. Along with its promise, however, the bioeconomy brings vulnerabilities and concerns.

Given the speed and importance of advances in the bioeconomy, the Office of the Director of National Intelligence asked the National Academies of Sciences, Engineering, and Medicine to convene a committee of experts to assess the scope of the U.S. bioeconomy and determine how to assess its economic value. The committee was also asked to identify

[1]This summary does not include reference citations. References for the information herein are provided in the full report.

potential economic and national security risks facing the bioeconomy and associated policy gaps, consider cybersecurity solutions for protecting data and other outputs of the bioeconomy, and determine mechanisms for tracking future advances and developments (see Box S-1 for the committee's complete Statement of Task). In responding to this request, this report provides an estimate for the value of the bioeconomy based on the committee's analysis. Additionally, the committee was tasked not with conducting a horizon scan of the bioeconomy, but with presenting and discussing methodologies that could be used to accomplish that task.

DEFINING THE U.S. BIOECONOMY

The U.S. bioeconomy is a broad and diverse enterprise that spans many scientific disciplines and sectors and includes a wide and dynamic range of stakeholders. Basic life sciences research often begins with public investment in research and training of scientists working in academic and federal research settings or within the research and development (R&D) departments of corporations. In addition to these traditional stakeholders, many large research institutions have spurred the development of local innovation ecosystems bringing in a wider range of stakeholders, including citizen science laboratories, incubator spaces, start-up companies, small businesses, and partnerships with larger industrial companies, as well as the network of providers of materials, tools, and expertise. The computing and information sciences, including machine learning, are dramatically accelerating the reach of the bioeconomy by making it possible to analyze and use biological data in new ways. Engineering principles and approaches are enabling automation and high-throughput experimentation, further accelerating the growth of the bioeconomy. Box S-2 provides further detail on how life sciences, biotechnology, engineering, and computing and information sciences serve as drivers of the bioeconomy. Currently, there is no consensus definition of a bioeconomy, resulting in differing interpretations of what activities are within the scope of a bioeconomy. A fundamental challenge is that bioeconomy activities span many sectors and scientific disciplines, are typically focused around a country's economic priorities, and combine subsets of traditional sectors measured in systems of national income accounts. Therefore, attempts to define and develop performance metrics for the bioeconomy and bioeconomy strategies invariably start with decisions about which economic activities to include as direct bioeconomy components.

Given the significant advances that have occurred since the National Bioeconomy Blueprint first articulated a U.S. definition in 2012, a new, comprehensive definition of the U.S. bioeconomy would enable the U.S. government to better assess the bioeconomy's current state and develop

strategies for supporting and safeguarding its continued growth. Such a definition could also guide the metrics and data collection efforts needed to track the bioeconomy's growth, conduct economic assessments, and enable policy makers to keep abreast of advances with the potential to pose new national or economic security challenges. Recognizing that a definition needs to be flexible enough to allow for the future inclusion of new developments, the committee developed a definition that does not limit the scope of the bioeconomy to particular sectors, technologies, or processes.

Recommendation 1: For purposes of demarcating the scope and reach of the U.S. bioeconomy and establishing a uniform framework for valuing the bioeconomy and its assets, the U.S. government should adopt the following definition of the U.S. bioeconomy:

> ***The U.S. bioeconomy is economic activity that is driven by research and innovation in the life sciences and biotechnology, and that is enabled by technological advances in engineering and in computing and information sciences.***

This definition encompasses all products, processes, and services that interact with or are built specifically for "research and innovation in the life sciences and biotechnology." It is intended to be flexible to anticipate the inclusion of new advances and applications within the life sciences and all of biotechnology. Additionally, the committee's definition references the impacts other disciplines have had on the life sciences. This definition thus fully embraces the convergence of many different scientific and engineering principles and domains with the life sciences. The transdisciplinary nature of the bioeconomy is key to its success and growth, enabling it to spread into economic sectors traditionally considered independent of the life sciences. Figure S-1 serves as a conceptual map of the U.S. bioeconomy.

MEASURING THE U.S. BIOECONOMY

Being able to adequately assess the economic contribution of the bioeconomy to the larger U.S. economy would raise awareness of the importance of the bioeconomy and the need to monitor and safeguard it. A full assessment of the inputs and outputs of the bioeconomy could also enable future analysis of how investment in basic research is tied to productivity, thus enabling better tracking of the outcomes of public investments. This enhanced tracking could also provide a means of understanding growing areas of the bioeconomy and potentially setting growth targets. Thus, better metrics for bioeconomy growth could serve as indicators of the health

BOX S-1
Statement of Task

An ad hoc committee of the National Academies of Sciences, Engineering, and Medicine will be convened to consider strategies for safeguarding and sustaining the economic activity driven by research and innovation in the life sciences, collectively known as the bioeconomy. In completing its task, the committee will outline the landscape of the U.S. bioeconomy, as well as:

- Outline existing approaches for assessing the value of the bioeconomy and identify intangible assets not sufficiently captured or that are missing from U.S. assessments, such as the value of generating and aggregating datasets.
- Provide a framework to measure the value of intangible assets, such as datasets.
- Outline metrics commonly used to identify strategic leadership positions in the global economy and identify areas in which the United States currently maintains leadership positions and is most competitive.
- Outline potential economic and national security risks and identify policy gaps pertaining to the collection, aggregation, analysis, and sharing of data and other outputs of the bioeconomy.
- Consider whether there are unique features of the bioeconomy that may require innovative cybersecurity solutions. In addition, determine if data or other intellectual property from the varied sectors of the bioeconomy (biomedical, agricultural, energy, etc.) require different safeguards or whether the same measures could be effective for all sectors. Also, determine if basic research requires different safeguarding mechanisms or whether practices effective for industry and manufacturing are applicable and sufficient for basic research.
- Develop ideas for horizon scanning mechanisms to identify new technologies, markets, and data sources that have the potential to drive future development of the bioeconomy. Consider whether additional strategies (beyond those identified for the existing components of the bioeconomy) might be needed to safeguard these new technologies and data, and assess their implications for innovation and biosecurity.

The committee will prepare a Consensus Study Report that identifies options for strategies to safeguard the bioeconomy and will provide its analyses of the pros and cons of each option. It will then recommend which option or options it believes will address the above issues and protect the technologies, data, and other intellectual property of the bioeconomy most effectively while sustaining innovation and growth.

BOX S-2
Four Drivers of the U.S. Bioeconomy

Life sciences: The subdisciplines of biology that make it possible to understand all life in the world are at the core of the bioeconomy. They specifically include the biological, biomedical, environmental biology, and agricultural sciences.

Biotechnology: Advances in technology that both apply and enable the life sciences, such as advanced sequencing, metabolic engineering, epigenetic modulation of gene expression, and gene editing, are all enabling the bioeconomy. They are being applied for a range of purposes, including curing disease, improving crop yields, and creating new products.

Engineering: Advances in biotechnology can require literally millions of experiments to bring a single new product to market. Robotics, microfluidics, tissue engineering, and cell culture are among the engineering processes used to aid in the production of bioeconomy products. Moreover, the application of engineering principles, such as design–build–test, to biology has greatly accelerated the field of synthetic biology.

Computing and information sciences: Computation allows mathematical modeling of experiments that can predict outcomes. Advanced computing techniques, such as machine learning, dramatically accelerate the ability to observe nonobvious patterns in large, complex datasets and to make "wise guesses," eliminating improbable experiments and pointing the way to the most promising leads.

of the sector, allow for an assessment of the impact of policy changes on the economic potential of the bioeconomy (or its subsectors), and help identify areas worth protecting from a security standpoint.

Based on the committee's calculations and available data, in 2016 the bioeconomy accounted for about 5.1 percent of U.S. gross domestic product (GDP). In dollar terms, this represents $959.2 billion.

In conducting this analysis, however, the committee found that many factors make it difficult to measure the contribution of the bioeconomy to the overall economy. As noted above, definitions of the bioeconomy that specify what it encompasses vary substantially; the bioeconomy is tied to both science and commercialization, which leads to divergent approaches for assessing its value; and data on the bioeconomy have substantial gaps.

Concepts used to value the bioeconomy present additional challenges. Social welfare analysis, which attempts to quantify benefits to producers and consumers, is a particularly demanding approach for valuing a sector as diffuse as the bioeconomy. In theory, one could value the bioeconomy as the sum of the private values or value added of all firms active in the

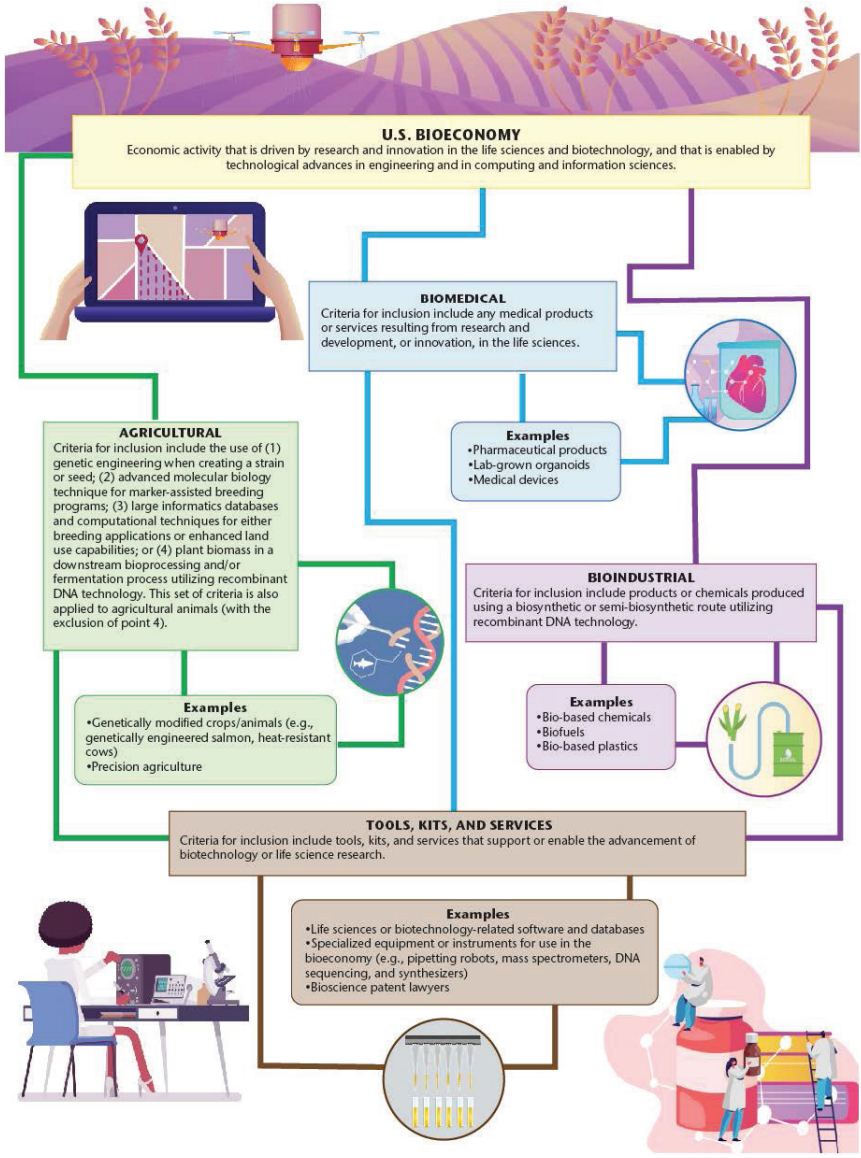


FIGURE S-1 Examples and explanations of highlighted sectors of the bioeconomy landscape that fall under the definition put forth in this report. The committee grouped the activities within the bioeconomy intro three primary domains: agricultural, biomedical, and bioindustrial. Additionally, the committee identified a cross-cutting category of tools, kits, and services.

sector. In practice, however, this is difficult, as many of the firms that operate in this sector are diversified, meaning their activities span a number of different areas, and it is difficult to isolate the bioeconomy-specific aspects of such firms.

In addition, existing data collection mechanisms for measuring economic activity are insufficient to monitor the bioeconomy holistically. This is due in part to the use of new biobased pathways to create products previously manufactured in sectors completely dissociated from biology.

In light of these impediments, the committee determined that a targeted and specialized framework for analyzing the value of the bioeconomy is needed (see Box S-3). The primary domains, or segments, of the

BOX S-3
Framework for Valuing the Bioeconomy

1. Set boundaries for the definition of the bioeconomy to identify primary segments of interest (see Chapter 2).
2. Identify subsets of the primary segments to be included, encompassing relevant bioeconomy-specific equipment investments (e.g., sequencing machines) and services (e.g., biotechnology patent and legal services) and intangible assets produced and/or curated for use by the sector (e.g., genomic databases).
3. Identify the relevant production data that map to the delineated bioeconomy segments.
   a. Table 3-2 (in Chapter 3) provides a mapping based on the North American Industry Classification System (NAICS) codes currently used by the U.S. Census Bureau to collect detailed data on the value of production.
      — Certain bioeconomy activities are inherently narrower than existing NAICS codes, and measuring those activities requires developing estimates based on auxiliary sources (or new NAICS codes), or building new aggregates from establishment-level survey or administrative microdata.
      — For each biobased production activity, determine the portion that is currently versus potentially (under existing technology) biobased (e.g., determine what percentage of plastics are made through a biobased process).
   b. Obtain estimates for value added for each relevant bioeconomy activity based on the same methods and data used in national accounts ("GDP by industry").
   c. Determine appropriate interindustry linkages and sources of supply (i.e., domestic versus foreign) and estimate relevant input-output "multipliers" based on these linkages.
4. The sum of value added estimates is the direct impact of bioeconomy production on the U.S. economy; the additional value added implied by input-output multipliers estimates the total contribution of the bioeconomy to the U.S. economy.

bioeconomy—agricultural, bioindustrial, and biomedical—are considered first as the major categories of activity encompassed by the bioeconomy definition presented above. However, when moving from a conceptual map based on scientific domains toward an economic mapping of the activities included in the bioeconomy, the groupings change to account for the current economic classification system. Thus, the committee needed to determine the subset of the primary segments for which economic activity data are captured. The following six segments are taken as an approximation of the bioeconomy, as best as can be determined from the available data, and recognizing that they incompletely capture the bioeconomy as the committee has defined it:

- genetically modified crops/products;
- biobased industrial materials (e.g., biobased chemicals and plastics, biofuels, agricultural feedstocks);
- biopharmaceuticals and biologics and other pharmaceuticals;
- biotechnology consumer products (e.g., genetic testing services);
- biotechnology R&D business services, including laboratory testing (kits), and purchased equipment services (e.g., sequencing services); and
- design of biological data-driven patient health care solutions, that is, precision medicine inputs (exclusive of patient care services per se and drugs counted elsewhere).

The committee offers the following recommendations to help expand and enhance data collection efforts so as to facilitate future valuations of the bioeconomy.

Recommendation 2: The U.S. Department of Commerce and the U.S. National Science Board should expand and enhance data collection efforts relevant to the economic contribution of the U.S. bioeconomy as defined by this committee.

Recommendation 2-1: The U.S. Department of Commerce and other relevant agencies and entities involved in the collection of U.S. economic data should expand their collection and analysis of bioeconomic data. The U.S. Department of Commerce should obtain input from partners in science agencies and from nongovernmental bioeconomy stakeholders to supplement and guide these efforts.

Recommendation 2-2: The existing North American Industry Classification System (NAICS) and North American Product Classification System (NAPCS) codes should be revised to more accurately

capture and track commercial activity and investments related to the biological sciences and track the growth of individual segments of the bioeconomy (e.g., biological production of chemicals and materials). In addition, the U.S. Department of Commerce's Office of Technology Evaluation should undertake a study aimed at richer characterization of the permeation of biologically based products, processes, and services in the U.S. economy. Such a study would greatly inform revisions of the NAICS and NAPCS codes. Additionally, the U.S. Census Bureau should refine and regularly collect comprehensive statistics on bioeconomic activities.

Recommendation 2-3: The Bureau of Economic Analysis of the U.S. Department of Commerce should lead the development of bioeconomy satellite accounts linked to central national accounts. These satellite accounts should include databases of biological information as assets and over time be expanded to include environmental and health benefits attributable to the bioeconomy.

Recommendation 2-4: The U.S. National Science Board should direct the U.S. National Science Foundation to undertake new data collection efforts and analyses of innovation in the bioeconomy for the *Science and Engineering Indicators* report so as to better characterize and capture the depth and breadth of the bioeconomy, with an emphasis on identifying indicators that provide insight into U.S. leadership and competitiveness.

STRATEGIES FOR SAFEGUARDING THE U.S. BIOECONOMY

A history of strong and sustained U.S. government investment in the life sciences, in computing and information sciences, and in engineering has powered the development of today's bioeconomy. Current U.S. leadership in this area will be challenged, however, as other countries invest in their bioeconomies at increasing rates. Falling behind in the application of computing and information sciences in the life sciences, in particular, could disrupt U.S. leadership in the increasingly global, data-driven bioeconomy. To retain the United States' world leadership position, strategies will be needed both to address risks to and from the U.S. bioeconomy and to ensure that it is supported and optimized for growth.

Risks to and from the U.S. bioeconomy identified by the committee in response to its Statement of Task include (1) risks that would harm the bioeconomy's continued growth or hamper the innovative ecosystem within which it currently operates; (2) risks from theft of, corruption of, asymmetries in, or constraints on access to intellectual property or key

bioeconomy information that would harm the U.S. bioeconomy, such as by conferring a competitive advantage on another party; and (3) risks from the misuse of bioeconomy outputs or entities.

Establishing Leadership and a Strategy for the U.S. Bioeconomy

While the committee recognizes that all of the stakeholders within the bioeconomy have a role to play, leadership and strategic direction are needed. Given the breadth of the bioeconomy across the many sectors discussed throughout this report, it is not surprising that life sciences research is distributed across many agencies and departments of the U.S. government. Moreover, no single agency has primary responsibility for the vitality of the biotechnology industry, or that of the greater bioeconomy. This disaggregated distribution poses a significant challenge for large-scale coordination, particularly when there is no clear candidate agency to take leadership. Each agency and department has a defined mission and associated scientific domain; therefore, no government agency has the mandate to monitor and assess the U.S. bioeconomy holistically, let alone determine a strategy for promoting and protecting it. In addition to hindering coordination, this distributed network of science agencies poses a challenge for comprehensively measuring the bioeconomy, as well as establishing a holistic horizon-scanning process to identify emerging developments in science and technology that could raise new issues or require new policy related to the bioeconomy. Given the lack of an obvious lead government agency for the bioeconomy, the committee concluded that a mechanism through which science, economic, and security agencies can bridge the current gaps in communication and coordination is needed.

Recommendation 3: The Executive Office of the President should establish a government-wide strategic coordinating body tasked with safeguarding and realizing the potential of the U.S. bioeconomy. To be successful, this coordinating body should be presided over by senior White House leadership, with representation from science, economic, regulatory, and security agencies. It should be responsible for relevant foresight activities and informed by input from a diverse range of relevant external stakeholders.

Recommendation 3-1: The coordinating body should develop, adopt, and then regularly update a living strategy with goals for sustaining and growing the U.S. bioeconomy. This strategy should be informed by an ongoing, formal horizon-scanning process within

each of the relevant science agencies, as well as by input from industry, nongovernmental organizations, and academia. Additionally, through this strategy, the coordinating body should identify and raise awareness of means through which the U.S. government can advance the bioeconomy, including such existing means as government procurement of biobased products.

Elements of a strategy for safeguarding and meeting the challenges that face the U.S. bioeconomy are detailed below.

Funding and Sustaining the Bioeconomy Research Enterprise

The U.S. bioeconomy relies on a robust and well-funded research enterprise that seeds innovation and supports a technically skilled and diverse workforce. Insufficient support for fundamental research will erode the United States' ability to produce breakthrough scientific results or achieve incremental learning that can also have direct economic application. Ultimately, this inadequate support will also erode the nation's ability to develop and recruit the world's best research talent, including domestic talent, particularly in competition with other countries that are investing heavily in their own bioeconomies.

Public investments in science and engineering research have played a foundational role in driving America's research enterprise. These investments have built the university research and education system that continually produces more doctoral graduates relative to any other country. Currently, the United States remains among the world's leaders in public investment in the biological sciences, but erosion in support for government investment is a concern that needs to be addressed. Analysis of past and current investments suggests that the rate of federal investment in this realm has become stagnant, while other countries are increasing their investments.

Recommendation 4: To maintain U.S. competitiveness and leadership within the global bioeconomy, the U.S. government should prioritize investment in basic biological science, engineering, and computing and information sciences. In addition, talent development, at all levels, to support these research areas should be a high priority for future public investment.

Building and Sustaining a Skilled Workforce

Insufficient federal funding for U.S. universities and bioeconomy training programs has the potential to diminish the ability to produce and

retain a skilled technical workforce. Increased federal support for science, technology, engineering, and mathematics (STEM) education and partnerships between community colleges and industry aimed at growing a technically skilled workforce could create employment opportunities in U.S. regions whose traditional employment opportunities may have changed. The development of biotechnology capabilities in rural areas and investments in training programs and facilities in those areas could enable new opportunities for those communities while growing the bioeconomy.

In addition to the importance of training a domestic bioeconomy workforce, the United States has historically benefited from the ability to attract students and scientists from around the world to its universities. International students constitute a significant fraction of the enrollments at U.S. colleges and universities, particularly in STEM disciplines at the graduate level, and foreign-born employees form a substantial component of the U.S. STEM research workforce. These researchers have contributed immensely to the vibrant research enterprise on which the nation currently depends. However, recent changes in visa policy and investigations into and new policies regarding researchers with potential ties to foreign governments, talent programs, and funding also have the potential to discourage talented researchers from around the world from coming to the United States or even collaborating with U.S.-based scientists.

Recommendation 4-1: The U.S. government should continue to support policies that attract and retain scientists from around the world who can contribute to the U.S. bioeconomy, recognizing that open academic engagement has been strongly beneficial to the U.S. scientific and technological enterprise, even as it inherently offers potential benefits to other countries as well. Policies intended to mitigate any economic and security risks posed by foreign researchers in U.S. research institutions should be formulated by U.S. security, science, and mission agencies working closely together, and through ongoing engagement with a group of recognized scientific leaders. Having this group able to be fully briefed on the threat environment will greatly facilitate these discussions, since access to classified, proprietary, or other nonpublic information may be needed.

Addressing Intellectual Property Threats

In addition to harms done to the U.S. bioeconomy by the nation's failure to take action to promote and support it, the bioeconomy is vulnerable to harm as a result of unfair or illegitimate actions of others, such as the theft of intellectual property. The U.S. bioeconomy has historically benefited from participation in an open, global, and collaborative scientific

environment that relies on the academic integrity of individuals and the willingness to adhere to research norms and values. Some federal officials have become increasingly concerned that the openness of the U.S. scientific enterprise puts its integrity and competitiveness at risk.

Safeguarding the U.S. bioeconomy while protecting innovation and growth could be facilitated by developing a more thorough understanding of the mechanisms by which the open conduct of and participation in fundamental scientific research drives proprietary innovation by entrepreneurs, both within the United States and among scientific and economic competitors, and conversely, of how restrictions on openness may affect the scientific research environment. Policy makers will have to strive for a balance that maximizes the benefits of scientific openness while protecting U.S. economic and security interests from countries that would exploit that openness unfairly.

Securing Value Chains and Examining Foreign Investments

The U.S. bioeconomy needs to be able to sustain itself by securing the value chains that fuel it. The continued development of biological routes to the production of previously non-biobased products will continue to disrupt existing value chains as the bioeconomy continues to permeate into new sectors. However, disruption of or risks to critical parts of bioeconomy value chains, such as supply shortages, interruptions in transport, or reliance on single sources, represent important risks to the nation. Reliance on single sources is particularly important if the source is based overseas and thus subject to changes in political relationships or other factors beyond U.S. control. Key components of bioeconomy value chains, key capabilities, and key sources of supply that are critical to the U.S. bioeconomy remain to be identified, as do mechanisms by which access to these assets can be ensured.

The transitional space where research is too applied for university-level development and yet still too risky to justify investment by commercial application represents an opportunity for venture capital to help start-up companies thrive. However, the source of venture capital funding for these early- to midstage developers may require more scrutiny, particularly given the increased trend of foreign investment in U.S. bioeconomy companies and start-ups. Examples exist of investments by nondomestic parties, either private capital or state backed, in U.S. bioeconomy businesses—both large, successful companies and smaller companies and start-ups—that were made with the goal of acquiring intellectual property.

The Committee on Foreign Investment in the United States (CFIUS) is responsible for reviewing potential foreign investments in and purchases

of U.S. companies. In August 2018, the Foreign Investment Risk Review and Modernization Act was signed into law, expanding CFIUS's purview. Given the specialized nature of the bioeconomy, the committee determined that CFIUS will likely require additional subject-matter expertise to adequately assess the implications of foreign investments in U.S. bioeconomy entities.

Recommendation 5: The U.S. government should convene representatives from its science and economic agencies who can access relevant classified information to provide security agencies with subject-matter expertise so as to (1) identify aspects of bioeconomy global value chains that are vital to U.S. interests and to which access must be ensured, and (2) assist the Committee on Foreign Investment in the United States in assessing the national security implications of foreign transactions involving the U.S. bioeconomy.

Prioritizing Cybersecurity and Information Sharing

Life sciences research is driven by the collection and analysis of large amounts of data that are often generated through the use of automated and network-connected instruments. The ability to process such data is increasingly enabled by high-throughput computational processing power and information exchange and storage capacity. Inadequate cybersecurity practices and protections expose the bioeconomy to significant new risks associated with these vast stores of data and networked automated instruments.

While large companies tend to be aware of traditional cyber concerns and have information technology infrastructures that provide protection, smaller companies and academic institutions may not always be aware that they are targets for cyber intrusions. Therefore, the committee concludes that all stakeholders (companies of all sizes, academic institutions, government agencies, and others) need to adopt best practices in cybersecurity in order to create an organizational culture that promotes and values cybersecurity. Adoption of these best practices could be accomplished in a number of different ways, such as with training for all researchers within the bioeconomy to increase awareness of cybersecurity threats and vulnerabilities; adoption of the National Institute of Standards and Technology's Cybersecurity Framework (which can be adapted for a wide range of organization sizes and types); and for some organizations, the appointment of chief information security officers.

Researchers receiving federal funding are often mandated to share their data in public databases, thereby expanding these vital databases rapidly. However, the potential for redundancy, inaccuracy, and even

conflicting entries poses a significant problem that is growing with the continued deluge of data. Attempts to merge, curate, and validate databases and redundant entries have demonstrated the considerable effort required; however, the potential net benefit for research is immense.

The bioeconomy relies on the use of open-source software, which means the software and its source code are openly available to anyone. However, the software industry has learned that making code open-source does little or nothing to guarantee its quality, robustness, and security. Open-source software introduces the potential for misuse, for example, if a malicious actor were to purposefully introduce a vulnerability into source code that enabled unauthorized access by third parties. These concerns could potentially be mitigated by establishing a more formal repository of open-source software for the bioeconomy, a formal regime for controlling changes to source code, a testing regimen for any changes to the code, and restrictions on who can make changes. Programs and incentives could be established to improve relevant software. Participation in an information-sharing group could additionally enable bioeconomy stakeholders to share experiences in detecting, mitigating, and preventing cyber intrusions, as they have done for many infrastructure sectors.

The following recommendations could help improve cybersecurity and information-sharing practices.

Recommendation 6: All bioeconomy stakeholders should adopt best practices for securing information systems (including those storing information, intellectual property, private-proprietary information, and public and private databases) from digital intrusion, exfiltration, or manipulation.

Recommendation 7: To protect the value and utility of databases of biological information, U.S. science funding agencies should invest in the modernization, curation, and integrity of such databases.

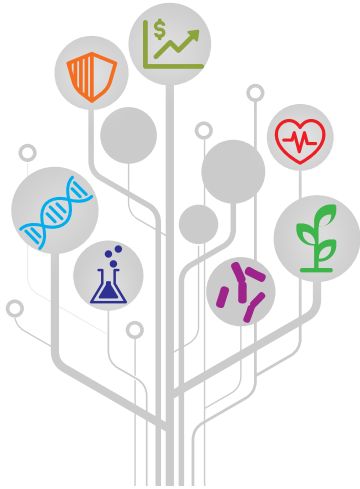
Recommendation 8: Bioeconomy stakeholders should pursue membership in one or more relevant Information Sharing and Analysis Centers or Information Sharing and Analysis Organizations, or consider creating a new sector-based information sharing organization for members of the bioeconomy. The Cybersecurity and Infrastructure Security Agency within the U.S. Department of Homeland Security should convene bioeconomy stakeholders to build awareness about relevant models for sharing information on cyberthreats. Those convened should consider whether an active repository is needed to host

and maintain key bioeconomy-related open-source software, algorithm components, and datasets.

OPPORTUNITIES FOR INTERNATIONAL ENGAGEMENT

The U.S. bioeconomy exists in the broader context of a global bioeconomy. Science is a global enterprise, and there is immense value to be gained from participating in a scientific enterprise that enables and embraces the free flow of ideas and discussion, the wide dissemination of published results, and collaboration across disciplines and borders. The benefits of such a system are available to all of the participants. Moreover, future challenges are going to be global in nature and will require a coordinated, global response. This will entail partnering with others who are actively growing and investing in their own bioeconomies, especially those who are likewise committed to open science, open economic development, and responsible research and innovation. However, while it is essential that the United States continue its role in international collaborations and play an active role in the global bioeconomy, uneven trade practices, a lack of reciprocity regarding sample- and data-sharing practices, and even regulatory regimes that make it more difficult for companies to bring their products to nondomestic markets still exist within this global enterprise. These practices, and others like them, have the potential to hinder the progress of research, the spread of innovative methods and ideas, and realization of the social and economic benefits of new products by undermining trust between collaborators.

Recommendation 9: Through such entities as the World Trade Organization and the Organisation for Economic Co-operation and Development, as well as through other bilateral and multilateral engagements, the U.S. government should work with other countries that are part of the global bioeconomy to foster communication and collaboration. The goals of such international cooperation would be to (1) drive economic growth, (2) reinforce governance mechanisms within a framework that respects international law and national sovereignty and security, and (3) create a level playing field.



1 INTRODUCTION

Advances in data sciences and applied mathematics that facilitate deep learning and machine learning for computational biology, along with advances in engineering that have enabled automation and high-throughput experimentation, are accelerating discovery within the life sciences.[1] The collective progress in these fields and the application of engineering principles to biology have in turn made possible the creation of new products based on biological processes, materials, and information. These products, and the research and development (R&D) that has created them, are changing the face of many industries and stimulating economic activity.[2] The term "bioeconomy," which has emerged over the past two decades as a way to conceptualize this economic activity, has differing attributions, and its meaning is continually evolving. Given that the term links biology and economic activity, moreover, its meaning differs across contexts and countries, reflecting the vast range of natural resources and technological strengths around the world. Despite these variations, more than 40 countries have recognized the potential of a bioeconomy to address a number of societal needs, and have articulated their intent to boost their own bioeconomies by incorporating the concept

[1]For the purposes of this report, the term "life sciences" is intended to encompass the biological, biomedical, environmental biology, and agricultural sciences.

[2]Disclaimer: Mention of examples of commercial companies or products made in the report are for illustrative purposes only and are not meant to imply endorsement by the committee; the National Academies of Sciences, Engineering, and Medicine; or any organizations providing funding for this study.

into their policy strategies (El-Chichakli et al., 2016), with the aim of leveraging the power of biology to enable new paths of creation and product development.

The United States has a long history of supporting and growing a vibrant life science research enterprise that is increasingly contributing to the growth of many economic sectors and has provided the nation with many benefits, such as improved health and environment and new and innovative products, generally leading to a better quality of life. The nation currently leads in many biotechnology[3] arenas, and also has tremendous natural and agricultural resources and sources of bio-derived feedstocks, both actual and potential, as well as technological capabilities.

The future of the U.S. bioeconomy offers promise of growth and prosperity, and improved quality of life through health and environmental benefits. For example, the bioeconomy offers potential new biobased pathways for creating chemicals, energy sources, and materials, enabling the replacement of traditional inputs such as petroleum feedstocks. Therefore, the bioeconomy can also contribute to climate change mitigation. However, this promise does not come without vulnerabilities and concerns. The many aspects of the bioeconomy rely heavily on a healthy and strong agricultural sector as both a consumer of and a contributing producer of bioeconomy goods and services. Moreover, the nation's clear leadership in biotechnology will be challenged as other countries make biotechnology investments at increasing rates (enabling them to advance their research and innovation base), reflecting a normal aspect of rivalry in the global economy, and recognizing that U.S. citizens will benefit from bioeconomy advances elsewhere even as the world benefits from U.S. advances. In light of these crucial benefits and the challenges they bring, the Office of the Director of National Intelligence (ODNI) requested that the National Academies of Sciences, Engineering, and Medicine (the National Academies) convene an ad hoc committee to consider how the U.S. bioeconomy can be safeguarded and sustained. This report presents the results of that study.

HISTORY OF THE U.S. BIOECONOMY

Several events led the United States to define and consider areas of structural importance to its own bioeconomy. The Great Recession, a period of significant general economic decline in world markets in the late 2000s and early 2010s, nucleated a series of efforts in the United States to stimulate economic recovery. During this time, the 2009 National Research

[3]Any technological application that uses biological systems, living organisms, biological processes, or derivatives thereof, to make or modify products or processes for specific use.

Council (NRC) report *A New Biology for the 21st Century* (NRC, 2009) was issued. This report describes the growing power of biology, and explains how biotechnology advances and has critical intersections with a number of scientific disciplines, including computing and engineering, addressing a broad range of human needs in such diverse areas as human health, food and nutrition, energy, and the environment (NRC, 2009). While that report is focused on social benefits, it also points to the deep ties between research innovation and economic benefits.

The following year, the U.S. government first acknowledged the need for strategic planning for the nation's bioeconomy. In their joint guidance memorandum on science and technology priorities for the fiscal year 2012 budget, the White House Office of Management and Budget and the Office of Science and Technology Policy (OSTP)[4] directed agencies to prioritize efforts to promote sustainable economic growth and job creation. Specifically, agencies were advised to "support research to establish the foundations for a 21st century bio-economy" in areas in which "advances in biotechnology and improvements in our ability to design biological systems have the potential to address critical national needs in agriculture, energy, health and the environment." This specific reference to biotechnology as a key feature of the future U.S. bioeconomy was aligned with the strengths of the nation's public and private research sectors in cutting-edge engineering biology and big data approaches to harness the potential of biological research for addressing national-scale challenges.

In addition to developing specific guidance for science and technology priorities in federal research to drive the U.S. bioeconomy, considerable effort was focused on reforming the patent system, stimulating economic growth, and enabling entrepreneurs to create new companies and new jobs. The resulting America Invents Act of 2011 (P.L. 112-29) addressed barriers that hindered the key industries of biotechnology, medical devices, and advanced manufacturing. The act was intended to accelerate innovation by providing a fast-track patent application process that would allow applicants to obtain a decision within 12 months, reducing the then-current patent backlog and, importantly, moving the U.S. patent system from a "first-to-invent" to a "first-inventor-to-file" system, thereby aligning U.S. patent policies with those of other patent systems around the world.

In 2012, the National Bioeconomy Blueprint[5] laid out strategic objectives that included strengthening relevant R&D efforts, advancing

[4]See https://www.whitehouse.gov/sites/whitehouse.gov/files/omb/memoranda/2010/m10-30.pdf.

[5]See https://obamawhitehouse.archives.gov/sites/default/files/microsites/ostp/national_bioeconomy_blueprint_april_2012.pdf.

discoveries from laboratory to market, reducing regulatory barriers, developing a 21st-century bioeconomy workforce, and fostering key public–private partnerships. It also highlighted the need to include biotechnology as a key driver of the U.S. bioeconomy strategy. Since its release, a number of major advances have accelerated the growth of the U.S. bioeconomy:

- The U.S. Department of Agriculture (USDA) expanded efforts to enable the procurement of biobased products through the BioPreferred Program,[6] and the BioRefinery Assistance Program (rebranded as the Biorefinery, Renewable Chemical, and Biobased Product Manufacturing Assistance Program[7]), and the Biomass Crop Assistance Program.[8]
- Major advances have occurred in engineering biology, including gene-editing approaches involving meganucleases, zinc fingers, transcription activator-like nucleases (TALENs), and clustered regularly interspaced short palindromic repeats (CRISPR).
- The launch of the Precision Medicine Initiative[9] occurred in 2016. It aims to use biological data and new analytics tools to derive inferences that can be applied to understand disease and develop diagnostics and treatments.
- In 2016, *The Billion Ton Biomass* report (USDA and the U.S. Department of Energy [DOE]) provided evidence and data on the potential for 1 billion tons of renewable biomass in the United States to give rise to 50 billion gallons of biofuels/25 percent of liquid transportation fuels, 50 billion pounds of biobased chemicals/products, reductions of 450 million tons of carbon dioxide (CO_2) emissions, and 1.1 million direct jobs/$250 million kept in the United States by 2030 (DOE, 2016; Rogers et al., 2017).
- In 2016, DOE established the first open, public biofoundry, the Agile BioFoundry,[10] to address precompetitive research challenges identified by industry.
- In 2016, the U.S. National Science Foundation launched its Big Idea initiative, including the Rules of Life Program.[11]

[6]See https://www.biopreferred.gov/BioPreferred/faces/pages/AboutBioPreferred.xhtml.

[7]Seehttps://www.rd.usda.gov/programs-services/biorefinery-renewable-chemical-and-biobased-product-manufacturing-assistance.

[8]See https://www.fsa.usda.gov/programs-and-services/energy-programs/BCAP/index.

[9]See https://obamawhitehouse.archives.gov/precision-medicine.

[10]See https://agilebiofoundry.org/how-we-got-here.

[11]See https://www.nsf.gov/news/special_reports/big_ideas/life.jsp.

- The release of the "2017 Update to the Coordinated Framework for the Regulation of Biotechnology" was aimed at increasing transparency, ensuring safety, streamlining regulatory processes, and accelerating the translation of bioinventions to market (EOP, 2017).
- In 2017, USDA released an interagency task force report outlining the need to increase public acceptance of biotechnology products, modernize and streamline the federal regulatory system for such products, and expedite their commercialization, all of which would improve the bioeconomy through biotechnology (USDA, 2017).
- In 2018, LanzaTech partnered with Pacific Northwest National Laboratory and Virgin Atlantic to develop and test new biojet fuel (Bauer and Burton, 2018).
- In 2019, the Biomass Research and Development Board of DOE and USDA issued *The Bioeconomy Initiative: Implementation Framework* (BRDB, 2019).
- In 2019, the Engineering Biology Research Consortium (EBRC) released its technical research roadmap, *Engineering Biology: A Research Roadmap for the Next-Generation Bioeconomy*,[12] which outlines technical themes and application sectors for engineering biology.

In addition to the previously mentioned 2009 NRC report *A New Biology for the 21st Century*, a number of more recent National Academies reports have elaborated specific sectors of biotechnology. Among them are the following:

- *Industrialization of Biology: A Roadmap to Accelerate the Advanced Manufacturing of Chemicals* (NRC, 2015) also speaks to specific aspects of chemical and fuel production via microbial biotechnology. It provides a roadmap for expanding the application of engineering biology in the production of chemicals.
- *Genetically Engineered Crops: Experiences and Prospects* (NASEM, 2016) showcases progress in the development and use of genetically engineered crops.
- *Preparing for the Future Products of Biotechnology* (NASEM, 2017) imagines possible developments on a 5- to 10-year horizon and considers regulatory frameworks needed to support them.

[12]See https://roadmap.ebrc.org.

- *Biodefense in the Age of Synthetic Biology* (NASEM, 2018) considers possible misuse of the powerful tools of synthetic biology.
- *Gaseous Carbon Waste Streams* (NASEM, 2019) identifies a number of feedstocks (CO_2, carbon monoxide [CO], methane [CH_4]) with the potential to drive the U.S. bioeconomy.

Beyond these publications, the NRC and the National Academies have worked with the science academies in the United Kingdom and China since 2013 to conduct a series of symposia titled Positioning Synthetic Biology to Meet the Challenges of the 21st Century. Additionally, the NRC and the National Academies convened three workshops in 2014, 2015, and 2016 exploring the bioeconomy, emerging technologies, and security concerns related to life sciences data.

The United States is not alone in seeing the economic advantages that can be derived from having a bioeconomy or from focusing investments in biotechnology. The Organisation for Economic Co-operation and Development, the European Commission, and several European countries individually have written their own related position papers and roadmaps. In 2012, the United Kingdom launched its Synthetic Biology Leadership Council, co-chaired by government and private-sector representatives. And China sees synthetic biology as having potential to accelerate economic growth, having developed its own long-term (20-year) plans and objectives. A detailed discussion of other nations' approaches to defining their bioeconomies and organizing their bioeconomy strategies can be found in Chapter 2.

The global bioeconomy, then, involves economic rivalry and cooperation among nations, in addition to significant scientific collaboration. Leadership in biotechnology has the potential to lead to economic advantage, whereas falling behind in biotechnology could have a cost, or at a minimum, the cost of lost opportunity.

ADVANCES IN BIOTECHNOLOGY AND THE LIFE SCIENCES

For the U.S. bioeconomy, the innovation process often begins with fundamental research. Fundamental discoveries in basic biology are cross-cutting and often agnostic to potential application areas. A revolution in life sciences is accelerating, powered by technologies for reading and writing genomes, facile gene and genome editing, and the leveraging of natural diversity through genome-wide association studies (GWASs) to identify the genes underlying desirable traits. Breakthroughs in systems biology and synthetic biology then provide an unprecedented capacity for engineering plants, animals, and microbes. This cycle of discovery

leading to technology that then amplifies discovery can be illustrated by the four examples described below. These are but a few examples of how the basic research enterprise of discovery science is now fueled by enabling technologies to such an extent that the rate of production of new knowledge continues to accelerate. Although the timescale for translation and advancement is different for different application areas, an important question is how the benefits of these knowledge gains can be translated most effectively into the bioeconomy and into positive impacts on society. The components of the innovation ecosystem that need to be in place to realize the potential of these scientific breakthroughs are discussed later in this chapter.

Example 1: Next-Generation Sequencing

In the last decade of the 20th century, conventional Sanger sequencing and then shotgun sequencing were used to generate the publicly funded sequences of the human genome and those of genetic model species, a painstaking labor involving international research consortia (Shendure et al., 2017). Over the first two decades of this century, next-generation deep-sequencing technologies have built on this foundation, using the previous era's sequences as definitive libraries against which to match short sequences produced by more modern instruments. Next-generation sequencing reduces the scale (size) of the sample, enabling massively parallel sequencing reactions—the simultaneous sequencing and analysis of millions of oligonucleotides (short strings of DNA bases). Thus, miniaturization of sequencing reactions allowed multiplexing of the number of reactions that can be run in a single experiment, dramatically increasing the speed of data acquisition (Shendure et al., 2017). It became possible to obtain complete genome sequences of prokaryotic organisms and the protein-coding regions of complex eukaryotic organisms on a routine basis and at a cost within the reach of a single investigator in a university. Gene and genome sequences and RNA transcripts can be compared between species, within a species, and within selected populations. Miniaturized equipment for DNA and RNA sequencing is available to further advance field work. And on the near horizon is instrumentation that can read the sequences of single molecules of DNA at the speed of DNA polymerization and in devices about the size of a thumb drive (Jupe et al., 2019).

Geneticists have used association mapping for more than a century to identify causative genes underlying a mutant phenotype. For such diseases as Huntington's disease and cystic fibrosis for which mutations in a single gene are causative, this is a reasonable approach. However, many human diseases, or desired traits in crops and animals, have a polygenic basis, meaning that more than one gene is likely responsible for the

disease or trait. The availability of thousands of genome sequences from a diseased population versus a healthy population of humans, plants, or animals has allowed identification of the suites of mutations that contribute to the risk of a particular disease. The more sequences are available, the greater is the statistical power in the association of genetic differences between the diseased and healthy populations with disease risk. These GWASs have identified tens or hundreds of new candidate genes[13] and biochemical pathways involved in autism, schizophrenia, obesity, and heart disease (Hall et al., 2016). Thus, the research community is beginning to understand the complex molecular bases of these diseases and to provide new therapeutic targets for drug development and diagnosis. Similarly, the application of GWASs to plant and animal populations is contributing to fundamental understanding of growth and development, resistance to stresses, and desired traits such as increased yield (Rai et al., 2019; Sun and Guan, 2018). The first GWAS study was published in 2005, and there are now about 4,000 curated studies with more than 130,000 associations (GWAS catalog[14]). Companies such as 23andMe and Ancestry DNA utilize GWAS predictions to provide reports to their individual consumers on genetic disease risks or other characteristics with a genetic basis. They can also use the data contributed by consumers in the aggregate to provide pharmaceutical companies with a rich dataset for their own GWAS analyses.

Example 2: Analytical Chemistry

New analytical methods have been developed that can identify the structures and concentrations of chemical species in complex mixtures in plant and microbial cells and in fermentation media, and those generated during the processing of lignocellulosic biomass. These complex mixtures can contain previously unknown compounds of a variety of characteristics (e.g., size, volatility, solubility, polarity, acidity, basicity, ionization energy, reactivity, and concentration). Both high-throughput and highly specialized analyses are now available, including methods based on high-resolution separations, novel ionization and dissociation methods, high-resolution mass spectrometry, and multistage tandem mass spectrometry (Aksenov et al., 2017).

The capability to inventory amounts and types of molecules beyond nucleic acids in living cells has had two major impacts. First, in basic

[13]GWASs have grown in the complexity of the gene networks they can connect. For example, a study examining the genetic basis for height recognizes the potential contributions of roughly 700 genes (Yengo et al., 2018).

[14]See https://www.ebi.ac.uk/gwas.

research, the accurate characterization of the protein and metabolite contents of living cells revealed the lack of correlation between transcript levels and their translated products, and then the primary and secondary metabolites synthesized by enzymes and enzyme complexes. Using proteomics and metabolomics data, computational modeling of biochemical pathways and their metabolic fluxes provides a systems-level view whereby hypotheses about the effects of perturbation of a component within the system can be tested in silico and then validated experimentally (Ideker et al., 2001). Second, as understanding of living systems increases, it becomes possible to move beyond a description of the system and its parts to the design of new parts and pathways and their genetic control. This mechanistic understanding is used to control native or synthetic pathways at the cell, tissue, and organismal levels. For example, the production of the antimalarial drug artemisinin by an engineered pathway in yeast rather than its native pathway in the plant *Artemisia annua*[15] was one of the first proofs of this concept (Paddon and Keasling, 2014), and was extended to the production of jet fuel precursors in *E. coli* (Liu et al., 2018).

Metabolic engineering and engineering biology, enabled by new analytical capabilities, are poised to enable use of a national resource of more than a billion tons of lignocellulosic biomass (DOE, 2011, 2016). Beyond ethanol produced from fermentation of biomass-derived sugars, early-stage research is mapping chemical, biochemical, and fast-pyrolytic conversion pathways to liquid hydrocarbon fuels similar to jet fuel, gasoline, or their components (McCann and Carpita, 2015). Lignin in intact woody biomass can be converted efficiently by chemical catalysts to methoxyphenols and then deoxygenated to propylcyclohexane (Parsell et al., 2015), and cellulose can be converted to 5-hydroxymethylfurfural (Yang et al., 2012). Plant species accumulate large amounts of carbon in the form of soluble phenylalanine-derived products and polyketides. Many of these compounds are conjugates of highly reduced aromatic molecules, and together with sugars and aromatics derived from plant cell walls, have the potential to be converted to next-generation fuels or co-products. In one example, Gevo Inc. has blended its renewable jet fuel, derived from wood waste, in test flights, but the current excitement about green (sustainable) chemistry has yet to translate to commercial application.

The bio-derived monomers, although abundant, in these examples represent a tiny proportion of the more than 400,000 kinds of molecules synthesized by living plant cells (Hur et al., 2013). Some natural plant

[15]The penultimate molecule in the reaction, artemisinic acid, can be produced using an engineered pathway in yeast. This molecule undergoes one final chemical reaction to produce the drug.

products have nutritional or pharmaceutical value and form the basis of foods, nutritional supplements (e.g., vitamins), and drugs, while others govern interactions of the plant with its environment (Farré et al., 2014; Fitzpatrick et al., 2012; Martin, 2013). The diversity of plant metabolism thus provides a foundation for metabolic engineering and engineering biology to meet societal goals in biofuels and bioproducts, as well as in food and feed production, biomedicine, and sustainability. Efficient production of target compounds requires systems-level understanding of metabolism and constraints, including trade-offs between carbon fluxes and cellular energy balances. Distributed network control, genetic redundancy, compartmentation of metabolic activities, and multicellularity together increase metabolic complexity in plants, making the design–build–test–improve engineering cycle more challenging than is the case for microbial systems. However, the ability to generate haploids and induce genome duplication such that plants are homozygous for all genomic loci is a breakthrough technology that significantly shortens the timeline for crop breeding (Kalinowska et al., 2019). Future technologies will facilitate both plant metabolic engineering itself and implementation strategies for engineering crops or plant cell cultures as bioproduction systems.

Example 3: Epigenetics

The cloning of Dolly the sheep by reproductive cloning was a technology landmark because it demonstrated that the nucleus of a differentiated cell could be reset to an undifferentiated state from which all cell lineages could be derived (Campbell et al., 1996). Since that landmark was achieved, it has become clear that development and disease in eukaryotic organisms are a function of both mutations in DNA and the modifications to the structure of chromatin that are made during a cell's or organism's lifetime, affecting the expression of the gene or genes in that area (epigenetics). The three pillars of epigenetics are methylation of cytosine in DNA; methylation, acetylation, and phosphorylation of the histone proteins around which the DNA is wound on nucleosomes; and RNA-mediated gene-silencing mechanisms that promote heterochromatin formation (Allis and Jenuwein, 2016). These DNA structures and modifications modulate gene expression to maintain the differentiated state of somatic cells. Some epigenetic marks on genomes are now known to occur as a result of chemical exposure, and some chemicals, including morphine, alcohol, and nicotine, show transgenerational effects (Bošković and Rando, 2018).

In fundamental studies leading to a Nobel Prize, the transcription factors that maintain the pluripotent state of embryonic stem cells were

identified, and shown to be necessary and sufficient to reset fully differentiated somatic cells to a pluripotent state (Takahashi and Yamanaka, 2006). The resulting cells are referred to as induced pluripotent stem cells (iPSCs). These iPSCs can then be induced to differentiate and form organoids, three-dimensional tissue cultures that recapitulate some of the complexity of animal or human organs (Franchini and Pollard, 2015). A patient's own skin cells, for example, can be reset to iPSCs and then triggered with a specific cocktail of transcription factors to form liver cells. This technology could eventually give rise to organ replacements fully compatible with a patient's own immune system (Kimbrel and Lanza, 2016). In combination with gene-editing technology, iPSCs and derived organoids have the potential to become patient-specific testbeds for drug responses.

Example 4: Gene and Genome Editing

Basic research investigating the mechanisms by which bacteria protect themselves from viral infections has led to a gene- and genome-editing technology for routine laboratory use (Sander and Joung, 2014). The CRISPR/Cas system uses noncoding RNAs to guide the Cas9 nuclease to induce site-specific double-stranded DNA cleavage. This DNA damage is repaired by cellular DNA repair mechanisms. A single guide RNA is generated to direct the Cas9 nuclease to the specific genomic location. Homologous recombination at the target site allows replacement of endogenous gene sequences with sequence variants encoded in DNA vectors (Lander et al., 2016). Careful genotyping is still required to identify the desired transformants and eliminate transformants resulting from off-target genetic modifications.

The ubiquity of gene editing using CRISPR/Cas9 in public and private research has arisen as the result of a noteworthy conjunction of circumstances. Other methods for creating changes to DNA, such as meganucleases, zinc-finger nucleases, and TALENs, were laborious because the protein recognition domain for each target sequence had to be designed and correctly expressed. Shifting from a system that depended on protein recognition of target DNA sequences to a system that depends on complementary DNA recognition of target DNA sequences simplified and resolved many of the underlying issues of molecular engineering. The rapidity of adoption of CRISPR/Cas9 by the research community is a function of the ease with which the technology can be used for the design of genetic modifications, the affordability of oligonucleotide synthesis, and the low cost of sequencing modified organisms.

One of the first human clinical trials using CRISPR/Cas9 gene editing is now ongoing in the United States for sickle cell disease, led by CRISPR

Therapeutics/Vertex Pharmaceuticals and Sangamo Therapeutics/Sanofi (Collins, 2019). The advantage of blood as an organ for gene editing is that it can be removed from a patient and reintroduced after the treatment. Red blood cells are short-lived and are continuously replaced by hematopoietic stem cells. Sickle cell disease is caused by a single base pair mutation in the beta-hemoglobin protein that reversibly binds oxygen in red blood cells. Unlike normal hemoglobin, the mutated hemoglobin polymerizes inside cells when deoxygenated, injuring the membrane of the cell and causing its rupture, and also distorting the shape of cells in a manner that leads to vaso-occlusion. Two strategies are being explored for efficient editing of induced hematopoietic stem cells (Sugimura et al., 2017) initially derived from sickle cell patients: the single nucleotide polymorphism in the beta-hemoglobin gene itself can be edited to the wild-type sequence, or a repressor of fetal hemoglobin can itself be mutated, leading to expression of normal fetal hemoglobin in adult patients (Bourzac, 2017). The U.S. Food and Drug Administration granted fast-track designation for the CRISPR-based treatment called CTX001 for this latter strategy.[16]

The convergence of the technologies described in the previous four examples for animal and human disease studies is now easy to imagine: the availability of DNA sequences permits GWAS analyses of healthy and diseased populations, from which candidate genes are inferred by genetic association. Expression of each of the tens or hundreds of candidate genes can be modulated using CRISPR/Cas9 technology in iPSCs and their derived organoids to test hypotheses of development and disease or to provide a testbed for evaluating therapeutic drugs.

FOUR DRIVERS OF THE U.S. BIOECONOMY

As noted earlier, definitions of the term "bioeconomy" vary across different contexts and countries. The focus of this study was on the U.S. bioeconomy, and so it is important before reporting the study's results to define what the term means in the U.S. context and for the purposes of this report. To this end, the committee identified four defining drivers of the U.S. bioeconomy (see Figure 1-1).

The first is the **life sciences**—the subdisciplines of biology that yield understanding of all forms of life on Earth. These subdisciplines include botany and agronomy, which focus on plants and agriculture, respectively; microbiology, which studies single-cell organisms; and

[16]See http://ir.crisprtx.com/news-releases/news-release-details/crispr-therapeutics-and-vertex-announce-fda-fast-track.

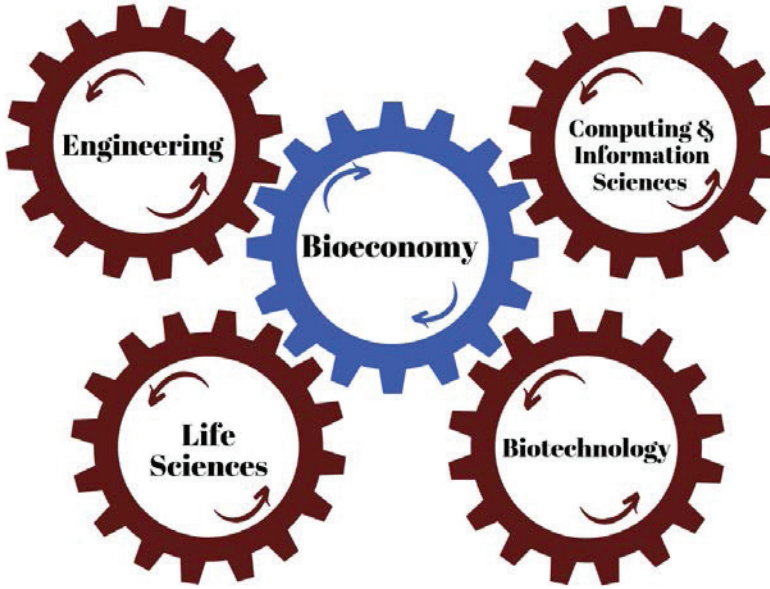


FIGURE 1-1 Four drivers of the U.S. bioeconomy.

environmental biology, the study of how plants and animals interact with their environment.

Second is **biotechnology,** which enables understanding biology at the level of genetics, the code for all living organisms. Advances in biotechnology have now made it possible not just to read the genetic code but to write it, and to engineer it to such purposes as curing a disease, improving a crop yield, or addressing an environmental need. Biotechnology advances have also enabled new methods for growing and analyzing cells and tissues, as well as for purifying enzymes for use in driving chemical reactions outside of their native cellular context. The four examples presented in the preceding section—next-generation sequencing, analytical chemistry, epigenetics, and gene and genome editing—are all powerful biotechnology tools that have accelerated the development of applications for the bioeconomy.

Advances in biotechnology require experimentation: to bring a biotechnology drug to market requires millions of experiments, and the same is true for a biotechnology crop or a new detergent enzyme. **Engineering** has made it possible to automate and miniaturize the experimental process, which enables high-throughput experimentation. Engineering advances in robotics and microfluidics support high-throughput techniques for product development, while advances in analytical techniques

enable use of smaller samples to derive results. In addition to robotics and microfluidics, examples of the use of engineering in the development and production of bioeconomy products include tissue engineering and cell culture, and advanced fermentation. Moreover, the application of engineering principles, such as design–build–test, to biology has greatly accelerated the field of synthetic biology.

Finally, **computing and information sciences** have made it possible to model experiments mathematically before they are run, as well as to predict outcomes. Experimentation results in large datasets—the "omics" (genomics, proteomics, metabolomics) data from humans, animals, plants, and microorganisms—along with the massive datasets associated with digital imaging. Today, advanced computing techniques such as machine learning are dramatically accelerating the ability to observe nonobvious patterns in large, complex datasets; to make "wise guesses," eliminating improbable experiments; and to continue to pursue the most promising leads. Biological datasets can also be paired with data from disparate sources, such as medical clinical observations, plant-breeding records, workplace exposure data, family histories, and lifestyle information from social media. Applications of artificial intelligence to these datasets will deepen and accelerate understanding of the interrelation between cause and effect, and between genotype and phenotype. It is this dimension that holds particular promise for the future of the U.S. bioeconomy, and it is also an area in which U.S. leadership in the increasingly global bioeconomy could be disrupted.

The committee's definition of the U.S. bioeconomy derives from its identification of the above four drivers:

> ***The U.S. bioeconomy is economic activity that is driven by research and innovation in the life sciences and biotechnology, and that is enabled by technological advances in engineering and in computing and information sciences.***

The U.S. bioeconomy thus defined rests on both the nation's natural resources and American ingenuity. It encompasses the products of biological processes and those based on biological feedstocks. It also includes the value chains that have formed to support these research and production activities, such as DNA sequencing services; "foundries" that produce domesticated "host" production organisms and DNA constructs; and consumables that are specific to biotechnology research, such as the ubiquitous 96-well plates and polymerase chain reaction kits. Perhaps most significant, this definition (and thus the bioeconomy) fully embraces the convergence of many different scientific and engineering principles and domains with the life sciences. The transdisciplinary nature of the

bioeconomy is key to its success and growth. It is this aspect that has enabled the bioeconomy to spread to sectors that have traditionally been completely independent of the life sciences.

CONSIDERATIONS IN SAFEGUARDING THE U.S. BIOECONOMY

In studying the overarching question of how to safeguard the U.S. bioeconomy, the committee identified a number of issues that need to be considered. For example, countries around the world rely on goods produced in the United States. Would the United States be comfortable relying on non-U.S. sources of therapies for treatment of U.S. citizens? Or non-U.S. sources for agricultural inputs needed to grow the nation's food supply? Or foreign biotechnology solutions to critical U.S. environmental concerns? The answers, of course, depend. What are the circumstances in each instance? What is the need? What are the potential consequences in human, environmental, economic, and security terms? On whom would the United States be dependent? What alternatives exist? While addressing all of these questions was beyond the scope of this study, many of the topics and concerns explored in this report feed into those discussions.

Even the process through which the U.S. bioeconomy develops is worthy of examination. The scientific process is collaborative by nature. Scientific processes in the United States are open by intent and by design; openness in science is always preferred. The science and technology enterprise of the U.S. bioeconomy advances through the sharing of data and information and through collaboration among scientists around the world. Sharing works to build scientific expertise while also saving resources, enabling many researchers (in academia or industry, within or outside of the United States) to benefit from initial investments and to validate discoveries made by others. For example, through the use and continued growth of public datasets, researchers can access information without needing to fund the re-creation of those datasets.

While sharing of data and information is desired, certain types of data associated with the U.S. bioeconomy pose privacy and security concerns. In medical research, for example, the privacy of patients' data, whether their electronic health records or their genomic sequence data, must be assured. This requirement limits what data can be shared and the manner in which it is shared. For instance, genetic data on the U.S. population and subpopulations may reveal vulnerabilities to specific diseases. Similarly, in the agricultural arena, genetic information on vital food crops could reveal vulnerability to disease or heightened susceptibility to genetically enhanced pathogens. Thus, the central issue arises of how to balance the intent to share openly with the legitimate privacy and security concerns involved.

Moreover, openness in science is extended with an expectation of reciprocity. A growing number of countries are restricting the sharing of genetic data or samples that can yield genetic information (conversely, others are sharing even more of these data and samples than is the United States). What is the appropriate response to this growing asymmetry and imbalance in openness in science?

These considerations represent the central impetus for this study.

STUDY CHARGE, SCOPE, AND APPROACH

As mentioned previously, in 2012 OSTP released the National Bioeconomy Blueprint, which laid the groundwork for characterizing and stimulating the U.S. bioeconomy. While the activity that followed focused on the scientific capabilities and potential for societal benefit, and there was some effort to characterize economic contributions in particular domains, little was done to holistically examine the value of the U.S. bioeconomy or assess the risks that relate to the bioeconomy. As a result, questions around the scope and scale of the bioeconomy persisted, a process by which to measure its value was never created, and concerns about the national strategic thinking and the ability to secure and protect the U.S. bioeconomy remained. The committee convened to conduct this study was tasked with delineating the scope of the U.S. bioeconomy, determining how to assess its economic value, identifying potential economic and national security risks related to the bioeconomy and associated policy gaps, considering cybersecurity solutions for protecting bioeconomy data and other outputs of the bioeconomy, and determining a mechanism for tracking future advances and developments within the bioeconomy. The committee's full Statement of Task is presented in Box 1-1. Importantly, the committee was not asked to determine the value of the bioeconomy; however, in the course of its information gathering, the committee did collect enough data to present a pilot experiment for bioeconomy valuation. The committee was also not tasked to conduct a horizon scan of future innovations in the bioeconomy; rather, this report describes methodologies that could be used to conduct and establish a process for horizon scanning and foresight to enable policy makers to stay abreast of developments in the bioeconomy.

To address its Statement of Task, the committee held three information-gathering workshops in Washington, DC, and three online webinars. Speakers at the workshops and webinars were selected to complement the broad expertise of the committee members and to represent various stakeholder groups within the U.S. bioeconomy. The speaker list for the workshops and webinars can be found in Appendix B. The discussions covered the breadth of the bioeconomy; various perspectives on how to

BOX 1-1
Statement of Task

An ad hoc committee of the National Academies of Sciences, Engineering, and Medicine will be convened to consider strategies for safeguarding and sustaining the economic activity driven by research and innovation in the life sciences, collectively known as the bioeconomy. In completing its task, the committee will outline the landscape of the U.S. bioeconomy, as well as:

- Outline existing approaches for assessing the value of the bioeconomy and identify intangible assets not sufficiently captured or that are missing from U.S. assessments, such as the value of generating and aggregating datasets.
- Provide a framework to measure the value of intangible assets, such as datasets.
- Outline metrics commonly used to identify strategic leadership positions in the global economy and identify areas in which the United States currently maintains leadership positions and is most competitive.
- Outline potential economic and national security risks and identify policy gaps pertaining to the collection, aggregation, analysis, and sharing of data and other outputs of the bioeconomy.
- Consider whether there are unique features of the bioeconomy that may require innovative cybersecurity solutions. In addition, determine if data or other intellectual property from the varied sectors of the bioeconomy (biomedical, agricultural, energy, etc.) require different safeguards or whether the same measures could be effective for all sectors. Also, determine if basic research requires different safeguarding mechanisms or whether practices effective for industry and manufacturing are applicable and sufficient for basic research.
- Develop ideas for horizon scanning mechanisms to identify new technologies, markets, and data sources that have the potential to drive future development of the bioeconomy. Consider whether additional strategies (beyond those identified for the existing components of the bioeconomy) might be needed to safeguard these new technologies and data, and assess their implications for innovation and biosecurity.

The committee will prepare a Consensus Study Report that identifies options for strategies to safeguard the bioeconomy and will provide its analyses of the pros and cons of each option. It will then recommend which option or options it believes will address the above issues and protect the technologies, data, and other intellectual property of the bioeconomy most effectively while sustaining innovation and growth.

define the bioeconomy, as well as measure the bioeconomy and assess the value of its various components; and the risks and benefits of the bioeconomy's various facets. These discussions served as the initial basis for the committee's deliberations, which were further informed by a review of the relevant literature.

ORGANIZATION OF THE REPORT

This report is organized into four parts addressing the key elements of the committee's Statement of Task: "Defining and Measuring the U.S. Bioeconomy" (Part I), "Understanding the Ecosystem and Identifying New Trends in the U.S. Bioeconomy" (Part II), "Understanding the Risks Associated with the U.S. Bioeconomy" (Part III), and "Strategies for Safeguarding the U.S. Bioeconomy" (Part IV).

In Part I, the committee presents its perspectives on how to define and measure the bioeconomy. Chapter 2, on defining the U.S. bioeconomy, details the various approaches used by countries around the world to define their bioeconomies and organize their bioeconomy strategies. That chapter also explores the committee's definition, presented earlier in this chapter, and its interpretation of how that definition sets the parameters of what is included in the U.S. bioeconomy. Chapter 3, on frameworks to measure the value of the U.S. bioeconomy, reviews the various approaches that can be used to assess the value of an economic sector and how those approaches can be applied to the U.S. bioeconomy. In light of its definition of the U.S. bioeconomy, the committee analyzes the data available for conducting such an assessment, undertaking a pilot experiment and examining the robustness of currently available data. In the process, steps were taken to identify data that are missing, not well characterized, or collected in such a way that it is difficult to incorporate them into an assessment of the value of the bioeconomy. The chapter presents a simplified framework for the process the committee undertook in this pilot experiment. Chapter 3 ends with a data-rich discussion of the current direction and status of the U.S. bioeconomy, examining national and private investments and indicators of innovation outcomes (e.g., patents, product approvals, sales). These U.S.-based data are examined in this chapter to prepare the reader for the global comparisons made in the subsequent chapter.

Chapter 4, on areas of leadership in the global economy, presents a detailed examination of the metrics commonly used to determine scientific and economic leadership within a domain. The metrics compared here include government investment in R&D, scientific output (captured in publications and patents), training indicators for students (degrees

granted), investments by private entities (corporations and venture capital firms), and the number of bioeconomy-relevant firms.

In Part II, the committee examines the innovation occurring within the bioeconomy and how new trends and developments can be tracked. Chapter 5, on the ecosystem of the U.S. bioeconomy, explores the nature of the life sciences research enterprise and the associated processes and structures that support and sustain it. This chapter includes examples of how advances in engineering and in computing and information sciences have created new opportunities for growth and development in life sciences research. Chapter 6, on horizon-scanning and foresight methods, assesses the various methodologies for bioeconomy-related horizon scanning and forecasting, providing examples of approaches relevant to the life sciences. The chapter also offers the committee's assessment of desirable elements for a future-thinking and horizon-scanning mechanism for the bioeconomy.

In Part III of the report, the committee explores the potential risks associated with the bioeconomy and provides its conclusions and recommendations for safeguarding the bioeconomy. Chapter 7, on economic and national security risks pertaining to the bioeconomy, outlines the various risks related to the U.S. bioeconomy, although the committee notes that much of this discussion does not differentiate economic from national security risks, which often cannot be decoupled. Within this chapter, the committee also examines policy mechanisms that can be used to address these risks, pointing out how these policies can be used to mitigate some risks but also may raise additional concerns through the potential for unintended consequences of particular actions.

In Part IV, Chapter 8, the committee presents its overall conclusions and recommendations, explaining their underlying logic and intent, and in some cases discussing different approaches for fulfilling the respective goals. The committee avoided being prescriptive and identified the relevant players when necessary. The committee's conclusions and recommendations encompass many of the subjects covered in this report, as the committee attempted to take a holistic approach when considering what elements to elevate to the top of its priority list. However, the recommendations are not presented in an order indicating priority, but rather in a manner designed to present a logical and holistic view of the bioeconomy.

REFERENCES

Aksenov, A. A., R. da Silva, R. Knight, N. P. Lopes, and P. C. Dorrestein. 2017. Global chemical analysis of biology by mass spectrometry. *Nature Reviews Chemistry* 1:0054.

Allis, C. D., and T. Jenuwein. 2016. The molecular hallmarks of epigenetic control. *Nature Reviews Genetics* 17(8):487–500.

Bošković, A., and O. J. Rando. 2018. Transgenerational epigenetic inheritance. *Annual Review of Genetics* 52:21–41.

Bourzac, K. 2017. Gene therapy: Erasing sickle-cell disease. *Nature* 549(7673):S28–S30.

BRDB (Biomass Research and Development Board). 2019. *The bioeconomy initiative: Implementation framework.* https://biomassboard.gov/pdfs/Bioeconomy_Initiative_Implementation_Framework_FINAL.pdf (accessed October 21, 2019).

Campbell, K. H. S., J. McWhir, W. A. Ritchie, and I. Wilmut. 1996. Sheep cloned by nuclear transfer from a cultured cell line. *Nature* 380:64–66.

Collins, F. 2019. A CRISPR approach to treating sickle cell. *NIH Director's Blog*, April 2. https://directorsblog.nih.gov/2019/04/02/a-crispr-approach-to-treating-sickle-cell (accessed August 30, 2019).

DOE (U.S. Department of Energy). 2011. *U.S. Billion-Ton Update*: *Biomass Supply for a Bioenergy and Bioproducts Industry.* R. D. Perlack and B. J. Stokes (Leads). ORNL/TM-2011/224. Oak Ridge, TN: Oak Ridge National Laboratory. https://www.energy.gov/sites/prod/files/2015/01/f19/billion_ton_update_0.pdf (accessed October 21, 2019).

DOE. 2016. *2016 billion-ton report: Advancing domestic resources for a thriving bioeconomy*, Vol. 1: *Economic availability of feedstocks*. http://energy.gov/eere/bioenergy/2016-billion-ton-report (accessed October 21, 2019).

El-Chichakli, B., J. von Braun, C. Lang, D. Barben, and J. Philp. 2016. Policy: Five cornerstones of a global bioeconomy. *Nature* 535(7611):221–223. doi: 10.1038/535221a.

EOP (Executive Office of the President). 2017. *Modernizing the regulatory system for biotechnology products: An update to the coordinated framework for the regulation of biotechnology*. https://obamawhitehouse.archives.gov/sites/default/files/microsites/ostp/2017_coordinated_framework_update.pdf (accessed August 30, 2019).

Farré, G., D. Blancquaert, T. Capell, D. Van Der Straeten, P. Christou, and C. Zhu. 2014. Engineering complex metabolic pathways in plants. *Annual Review of Plant Biology* 65:187–223.

Fitzpatrick, T. B., G. J. Basset, P. Borel, F. Carrari, D. DellaPenna, P. D. Fraser, H. Hellmann, S. Osorio, C. Rothan, V. Valpuesta, C. Caris-Veyrat, and A. R. Fernie. 2012. Vitamin deficiencies in humans: Can plant science help? *Plant Cell* 24:395–414.

Franchini, L. F., and K. S. Pollard. 2015. Genomic approaches to studying human-specific developmental traits. *Development* 142(18):3100–3112.

Hall, M. A., J. H. Moore, and M. D. Ritchie. 2016. Embracing complex associations in common traits: Critical considerations for precision medicine. *Trends in Genetics* 32(8):470–484. doi: 10.1016/j.tig.2016.06.001.

Hur, S. J., S. Yuan Lee, Y.-C. Kim, I. Choi, and G.-B. Kim. 2013. Effect of fermentation on the antioxidant activity in plant-based foods. *Food Chemistry* 160:346–356.

Ideker T., V. Thorsson, J. A. Ranish, R. Christmas, J. Buhler, J. K. Eng, R. Bumgarner, D. R. Goodlett, R. Aebersold, and L. Hood. 2001. Integrated genomic and proteomic analyses of a systematically perturbed metabolic network. *Science* 292(5518):929–934.

Jupe, F., A. C. Rivkin, T. P. Michael, M. Zander, S. T. Motley, J. P. Sandoval, R. K. Slotkin, H. Chen, R. Castanon, J. R. Nery, and J. R. Ecker. 2019. The complex architecture and epigenomic impact of plant T-DNA insertions. *PLoS Genetics* 15(1):e1007819. doi: 10.1371/journal.pgen.1007819.

Kalinowska, K., P. Lenartowicz, J. Namieśnik, and M. Marć. 2019. Analytical procedures for short chain chlorinated paraffins determination—How to make them greener? *Science of the Total Environment* 671:309–323.

Kimbrel, E. A., and R. Lanza. 2016. Pluripotent stem cells: The last 10 years. *Regenerative Medicine* 11(8):831–847.

Lander, N., M. A. Chiurillo, and R. Docampo. 2016. Genome editing by CRISPR/Cas9: A game change in the genetic manipulation of protists. *Journal of Eukaryotic Microbiology* 63(5):679–690. doi: 10.1111/jeu.12338.

Liu, C.-L., T. Tian, J. Alonso-Gutierrez, B. Garabedian, S. Wang, E. E. K. Baidoo, V. Benites, Y. Chen, C. J. Petzold, P. D. Adams, J. D. Keasling, T. Tan, and T. S. Lee. 2018. Renewable production of high density jet fuel precursor sesquiterpenes from *Escherichia coli*. *Biotechnology for Biofuels* 11(1):285.

Martin, C. 2013. The interface between plant metabolic engineering and human health. *Current Opinion in Biotechnology* 24:344–353.

McCann, M. C., and N. C. Carpita. 2015. Biomass recalcitrance: A multi-scale, multi-factor, and conversion-specific property. *Journal of Experimental Botany* 66(14):4109–4118.

NASEM (National Academies of Sciences, Engineering, and Medicine). 2016. *Genetically engineered crops: Experiences and prospects.* Washington, DC: The National Academies Press. https://doi.org/10.17226/23395.

NASEM. 2017. *Preparing for future products of biotechnology*. Washington, DC: The National Academies Press. https://doi.org/10.17226/24605.

NASEM. 2018. *Biodefense in the age of synthetic biology*. Washington, DC: The National Academies Press. https://doi.org/10.17226/24890.

NASEM. 2019. *Gaseous carbon waste streams utilization: Status and research needs*. Washington, DC: The National Academies Press. https://doi.org/10.17226/25232.

NRC (National Research Council). 2009. *A new biology for the 21st century*. Washington, DC: The National Academies Press. https://doi.org/10.17226/12764.

NRC. 2015. *Industrialization of biology: A roadmap to accelerate the advanced manufacturing of chemicals*. Washington, DC: The National Academies Press. https://doi.org/10.17226/19001.

Paddon, C. J., and J. D. Keasling. 2014. Semi-synthetic artemisinin: A model for the use of synthetic biology in pharmaceutical development. *Nature Reviews Microbiology* 12(5):355–367.

Parsell, T., S. Yohe, J. Degenstein, T. Jarrell, I. Klein, E. Gencer, B. Hewetson, M. Hurt, J. I. Kim, H. Choudhari, B. Saha, R. Meilan, N. Mosier, F. Ribeiro, W. N. Delgass, C. Chapple, H. I. Kenttämaa, R. Agrawal, and M. M. Abu-Omar. 2015. A synergistic biorefinery based on catalytic conversion of lignin prior to cellulose starting from lignocellulosic biomass. *Green Chemistry* 17(3):1492–1499.

Rai, A., M. Yamazaki, and K. Saito. 2019. A new era in plant functional genomics. *Current Opinion in Systems Biology* 15:58–67.

Rogers, J. N., B. Stokes, J. Dunn, H. Cai, M. Wu, Z. Haq, and H. Baumes. 2017. An assessment of the potential products and economic and environmental impacts resulting from a billion ton bioeconomy. *Biofuels, Bioproducts and Biorefining* 11:110–128. doi: 10.1002/bbb.1728.

Sander, J. D., and J. K. Joung. 2014. CRISPR-Cas systems for editing, regulating and targeting genomes. *Nature Biotechnology* 32(4):347–355.

Shendure, J., S. Balasubramanian, G. M. Church, W. Gilbert, J. Rogers, J. A. Schloss, and R. H. Waterston. 2017. DNA sequencing at 40: Past, present and future. *Nature* 550(7676):345–353.

Sugimura, R., D. K. Jha, A. Han, C. Soria-Valles, E. L. da Rocha, Y. F. Lu, J. A. Goettel, E. Serrao, R. G. Rowe, M. Malleshaiah, I. Wong, P. Sousa, T. N. Zhu, A. Ditadi, G. Keller, A. N. Engelman, S. B. Snapper, S. Doulatov, and C. Q. Daley. 2017. Haematopoietic stem and progenitor cells from human pluripotent stem cells. *Nature* 545(7655):432–438.

Sun, H.-Z., and L. L. Guan. 2018. Feedomics: Promises for food security with sustainable food animal production. *TrAC Trends in Analytical Chemistry* 107:130–141.

Takahashi, K., and S. Yamanaka. 2006. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. *Cell* 126(4):663–676.

USDA (U.S. Department of Agriculture). 2017. *Report to the President of the United States from the Task Force on Agriculture and Rural Prosperity*. https://www.usda.gov/sites/default/files/documents/rural-prosperity-report.pdf (accessed October 21, 2019).

Yang, Y., C. W. Hu, and M. M. Abu-Omar. 2012. Conversion of carbohydrates and lignocellulosic biomass into 5-hydroxymethylfurfural using $AlCl_3 \cdot 6H_2O$ catalyst in a biphasic solvent system. *Green Chemistry* 14(2):509–513.

Yengo, L., J. Sidorenko, K. E. Kemper, Z. Zheng, A. R. Wood, M. N. Weedon, T. M. Frayling, J. Hirschhorn, J. Yang, and P. M. Visscher. 2018. Meta-analysis of genome-wide association studies for height and body mass index in ~700000 individuals of European ancestry. *Human Molecular Genetics* 27(20):3641–3649. doi: 10.1093/hmg/ddy271.

PART I

DEFINING AND MEASURING THE U.S. BIOECONOMY

The first part of this report is focused on defining the U.S. bioeconomy; exploring the methods, data, and analysis needed to measure its value; and understanding how to determine the U.S. leadership position within the global bioeconomy.

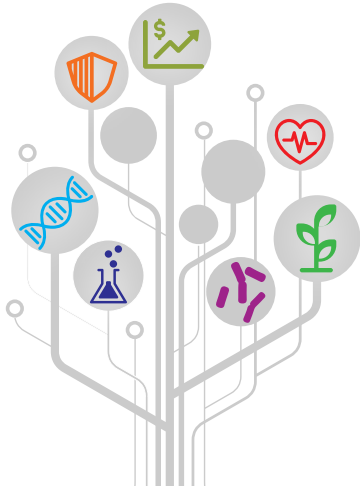
Chapter 2 examines the various conceptual approaches used around the world to understand and define the term "bioeconomy." The committee characterizes the various bioeconomy definitions into three different visions: a biotechnology vision, a bioresource vision, and a bioecology vision. With this context, the chapter then refocuses on the committee's new definition, a comprehensive and flexible one that allows for future developments, and uses it to articulate the bounds of the U.S. bioeconomy. This discussion directly addresses the element of the committee's Statement of Task requesting that the committee "outline the landscape of the U.S. bioeconomy."

Chapter 3 undertakes a detailed discussion of how to measure the value of the U.S. bioeconomy, responding directly to the first two bullets of the Statement of Task. First, the chapter examines the characteristics of the bioeconomy that set it apart from other sectors. Then, the chapter considers approaches for both identifying intangible assets and determining the value of the U.S. bioeconomy, in accordance with the committee's definition. This discussion culminates in a pilot valuation experiment that applies the valuation framework set forth in this chapter using the available data, while pointing out the data elements that are missing or difficult to parse out in a way that is specific to the bioeconomy. This

discussion demonstrates a need for new data collection and analysis capabilities. Lastly, the chapter examines the trends and direction of the bioeconomy by analyzing national and private investments in research and development, as well as innovation outcomes from the bioeconomy.

Chapter 4 then examines areas of U.S. leadership in the context of the global bioeconomy. To this end, the committee compares government investments, scientific output metrics, scientific training, and private innovation inputs.

These three chapters set the foundation for the remainder of the report by articulating the scope, size, and value of the U.S. bioeconomy, while providing a rationale for how to determine those endpoints.



2 DEFINING THE U.S. BIOECONOMY

Summary of Key Findings

- Currently, there is no consensus on the definition of a bioeconomy, although many definitions share key common elements (such as substituting biological resources for fossil fuels to produce electricity, fuels, and manufactured goods).
- Definitions of a bioeconomy are evolving and will continue to change over time.
- A fundamental challenge in defining a bioeconomy is that it is not a single economic sector or grouping of sectors. Rather, its activities span sectors and are combinations of subsets of traditional sectors measured in systems of national income accounts.
- Attempts to define a bioeconomy and develop performance metrics and strategies for that bioeconomy invariably lead to decisions about which economic activities to include and exclude as direct bioeconomy components.
- More than 40 countries have created formal strategies for promoting their bioeconomies.
- National bioeconomy definitions and strategies vary with countries' technological capacity, natural resource base, and economic comparative advantage.
- In taking steps to monitor the performance of their bioeconomies, countries have turned from general characterizations of the bioeconomy toward quantitative measurement of the bioeconomy's economic contribution and growth. The topic of measuring a bioeconomy and understanding its performance metrics is discussed in detail in Chapter 3.

Interest in the concept of a bioeconomy—as a research topic and as a focus of economic, technology, and security policy—has grown rapidly over the past 20 years. The number of research publications referring to the bioeconomy (or closely related terms) began to grow in the mid-2000s (Birner, 2018; Bugge et al., 2016; Golembiewski et al., 2015; Nobre and Tavares, 2017) (see Figure 2-1). To date, more than 40 countries have developed formal strategies for promoting their bioeconomies (Dietz et al., 2018), in addition to efforts to harmonize national measurements of the bioeconomy and its contribution to the overall economy (Bracco et al., 2018; EC, 2018; Parisi and Ronzon, 2016).

What accounts for this recent surge in interest and activity? After all, humans have been growing crops, raising livestock, brewing beer, burning wood for fuel, and using timber for building for millennia. And humans have been gathering biological materials to test their nutritional and medicinal potential for even longer. Economic activity surrounding the use of biological resources remains a fundamental part of modern economies. Indeed, agriculture, forestry, and fisheries (along with mining) are referred to as "primary sectors" of national economies.

Three factors have contributed to this recent interest in the bioeconomy. First, advances in biological sciences and biotechnology hold the

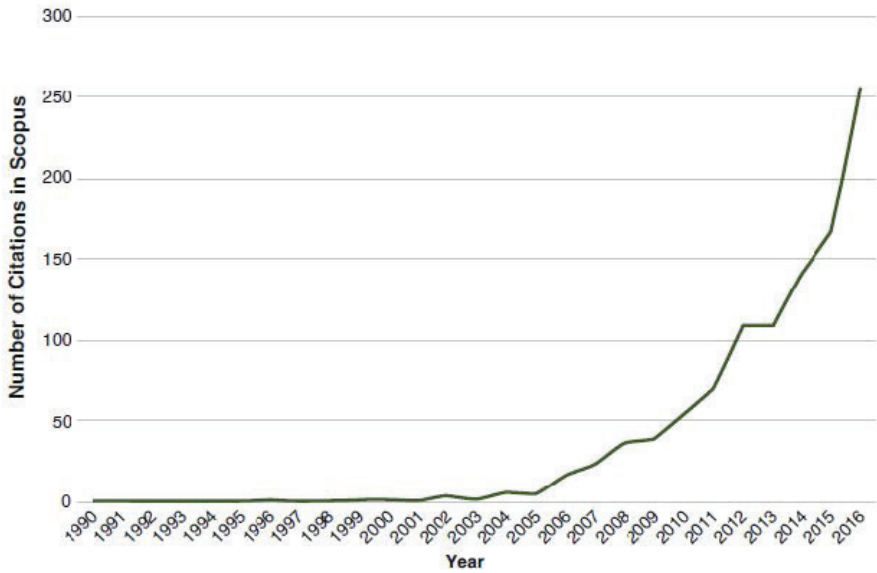


FIGURE 2-1 Number of publications listed in Scopus with "bio-based economy," "biobased economy," "bioeconomy," or "bio-economy" in their titles, abstracts, or keywords. SOURCE: Birner, 2018.

promise of valuable, new commercial applications, as well as new paths toward existing product types. Three developments in particular—genetic engineering, DNA sequencing, and high-throughput molecular operations facilitated by robotic technologies—"transformed the practice and potential of biological research" (U.S. OSTP, 2012, p. 7). Thus, biotechnology has become a new area of international technological and economic competition (Gronvall, 2017; Langeveld, 2015; Li et al., 2006; Meyer, 2017; U.S. OSTP, 2012). Second, substitution of exhaustible fossil fuels with renewable biological resources to produce electricity, fuel, and chemical-based manufactured products became a priority to serve a variety of policy objectives in many countries (de Besi and McCormick, 2015; Dietz et al., 2018; McCormick and Kautto, 2013; Staffas et al., 2013). These objectives included rural economic development, energy self-reliance, and climate change mitigation. Third, genetic materials and biodiversity have increasingly been viewed as inputs to the discovery and production of new pharmaceuticals and other biobased products (Barbier and Aylward, 1996; Ivshina and Kuyukina, 2018; Perrings et al., 2009; Sasson and Malpica, 2018; Sedjo, 2016; Simpson et al., 1996; Trigo et al., 2013; Valli et al., 2018). Genetic resources serve both as a source of materials and as blueprints for the design of new commercial compounds (Mateo et al., 2001).

Dr. Bernadine Healy, then director of the National Institutes of Health, used the specific term "the bioeconomy" in speeches dating back to 1992 (Healy, 1992a,b; Nerlich, 2015). In her 1994 commencement address at Vassar College, Healy (1994, p. 13) observed:

> A revolution in the life sciences will also go way beyond medicine into agriculture, chemical production, environmental sciences, micro-electronics. Biotechnology will be creating jobs that we don't even have names for yet. And they will be high-paying, high-demand jobs—and intellectually satisfying ones. New industries will emerge that will be a growing source of national economic strength and world leadership. Some have gone so far as to suggest that the twenty-first century will be based on a bioeconomy.

Juan Enríquez and Rodrigo Martinez are credited with later using the term "bioeconomy" at a 1997 scientific conference (Birner, 2018; Maciejczak and Hofreiter, 2013; Petersen and Krisjansen, 2015; von Braun, 2015; von Hauff et al., 2016). These sources also cite a 1998 article in *Science* by Enríquez, "Genomics and the World's Economy," that, although not using the term "bioeconomy" specifically, emphasizes the scientific, technological, and economic implications of innovations in genomics that allowed for the study, design, and construction of economically important molecules (Enríquez, 1998).

The article by Enríquez (1998) emphasizes key economic implications of advances in genomics. Boundaries between the agribusiness, pharmaceutical, and chemical industries were blurring as the potential for complementary technological applications spurred a wave of corporate mergers and acquisitions. According to Enríquez, "The objective of the life science company is no longer to generate breakthroughs in a single area such as medicine, chemicals, or food, but to become a dominant player in all of these." Indeed, companies with histories in agricultural, chemical, and pharmaceutical production merged, reorganized, and acquired seed companies (and their stocks of crop germplasm) to expand into the development and sale of genetically modified (GM) crop varieties (Bonny, 2014; Deconinck, 2019; Howard, 2015; Maisashvili et al., 2016; Schimmelpfennig et al., 2004). These changes in scientific and business models would transform the energy sector, as plant-based energy sources would begin to substitute for fossil fuels. Enríquez heralds the rise "of a new economic sector, the life sciences."

Over the past 25 years, U.S. agriculture has illustrated the transformations that Enríquez envisioned, with significant changes in both how new crop varieties are developed and how crops are used. Sales of GM crops now account for roughly half of total U.S. crop sales (see Chapter 3 for more detail). The U.S. energy sector has also seen the shift toward plant-based fuels that Enríquez envisioned. Today, more than one-third of the corn and soybean crops produced in the United States is used for fuel (see Chapter 3). The United States is now the world's leading producer of biofuels, followed by Brazil and the European Union (EU) (Le Feuvre, 2019).

The remainder of this chapter explores different definitions of the bioeconomy used by governments and academics, which can be characterized according to three different visions of a bioeconomy's purpose: a biotechnology vision, a bioresource vision, and a bioecology vision. The chapter then reviews the approaches taken to define a landscape of what is included in the bioeconomy. Next, the committee reiterates from Chapter 1 its definition of the U.S. bioeconomy and presents a high-level review of what the U.S. bioeconomy landscape looks like based on this definition. The chapter ends with the committee's conclusions with respect to defining the U.S. bioeconomy.

THE BIOECONOMY: ALTERNATIVE DEFINITIONS

Around the world, government bodies, scholars, and private business organizations continue to develop new definitions of the term "bioeconomy" to communicate which life sciences–related economic activity they are referring to. As noted in Chapter 1, there currently is no globally accepted consensus definition of the term. The wording some entities use is vague, with the bioeconomy being referred to as "a notion" (Bugge et al., 2016), "an

emerging concept" (Wesseler and von Braun, 2017), and a "policy concept" (Birner, 2018), while "the definitions have shown to evolve in a relatively short period of time" (McCormick and Kautto, 2013), with different definitions being classified in terms of different "visions" (discussed below) (Bugge et al., 2016; Pfau et al., 2014). Yet, "it remains unclear what the bioeconomy is" (Scordato et al., 2017), and "there seems to be little consensus concerning what bioeconomy actually implies" (Bugge et al., 2016).

Some earlier studies discuss or provide tables and lists of alternative definitions of the bioeconomy (e.g., Bugge et al., 2016; Maciejczak and Hofreither, 2013; Meyer, 2017; Staffas et al., 2013). Box 2-1 provides a sample of bioeconomy definitions from publications of national governments and international organizations. This set is not exhaustive, but representative of the variety of definitions employed. A common theme is the use of biological resources. Definitions vary in terms of the emphasis they place on new uses of these resources (e.g., energy, material production) and whether traditional activities (e.g., food production) are considered. They also vary in the explicit use of the term "biotechnology," but that term is usually included.

Many countries have developed separate strategies for promoting biotechnology and biobased production, which relies on the substitution of biological resources for fossil fuels. Over time, these separate strategies have been combined under an overarching concept of the bioeconomy (Staffas et al., 2013). As the number of definitions of the bioeconomy grows, the value of cataloguing definitions diminishes. There has been a shift in emphasis from simply listing definitions to studying the variation in definitions themselves to understand common and divergent components (Bracco et al., 2018; Bugge et al., 2016; Pfau et al., 2014; Staffas et al., 2013). Some of this research has included bibliometric analysis of publications on the bioeconomy (Birner, 2018; Bugge et al., 2016; D'Amato et al., 2017; Golembiewski et al., 2015; Nobre and Tavares, 2017). Bibliometric studies provide detailed analyses regarding which fields of science, regions, and institutions are conducting research defining the bioeconomy.

The committee chose to characterize different definitions based on an approach adopted from Bugge and colleagues (2016), who catalog the definitions in terms of three different visions of a bioeconomy's purpose: (1) a biotechnology vision, (2) a bioresource vision, and (3) a bioecology vision (Devaney and Henchion, 2018; Scordato et al., 2017; Wreford et al., 2019):

- Under the biotechnology vision, activities in the bioeconomy center around generating scientific knowledge enabled by the purposeful manipulation of DNA, with production processes operating at the molecular level, the commercialization of such

BOX 2-1
Global Examples of Definitions of the Bioeconomy

Argentina
"Sustainable production of goods and services through the use or transformation of biological resources" (Bracco et al., 2018; MINAGRO, 2016).

Australia
"The emerging concept of sustainable production and conversion of biomass (organic matter) for a range of food, health, fiber, and other industrial products as well as energy" (Bracco et al., 2018).

Brazil
"The term bioeconomy refers to 'the generation of innovative products and services based on the country's natural resources and ecosystem services.' While the 'expanded bioeconomy' is defined 'as a set of economic activities related to the invention, development, production and use of biological products and/or processes for the production of renewable energy, materials and chemicals'" (German Bioeconomy Council, 2018).

China
In China, political interest in the bioeconomy relates strongly to the promotion of biotechnology development. For example, biotechnology development was a prominent topic in the 11th, 12th, and 13th Five-Year Plan for Economic and Social Development (German Bioeconomy Council, 2018).

European Commission
"The bioeconomy encompasses the production of renewable biological resources and their conversion into food, feed, bio-based products and bioenergy. It includes agriculture, forestry, fisheries, food, and pulp and paper production, as well as parts of the chemical, biotechnological, and energy industries. Its sectors have a strong innovation potential due to their use of a wide range of sciences (life sciences, agronomy, ecology, food science, and social sciences), enabling and industrial technologies (biotechnology, nanotechnology, information and communication technologies, and engineering), and local and tacit knowledge" (Haarich et al., 2017).

Finland
"The bioeconomy is an economy that relies on renewable natural resources to produce food, energy, products, and services. The bioeconomy strives to reduce dependence on fossil natural resources, to prevent biodiversity loss, and to create new economic growth and jobs in line with the principles of sustainable development" (Natural Resources Institute Finland, 2019).

Food and Agriculture Organization of the United Nations
The bioeconomy can be defined as "the knowledge-based production and utilization of biological resources, biological processes and principles to sustainably provide goods and services across all economic sectors." It involves three elements: (1) Utilization of renewable biomass and efficient bioprocesses to achieve a sustainable production; (2) Utilization of enabling and converging technologies, including biotechnology; and (3) Integration across applications such as agriculture, health, and industry (Bracco et al., 2018).

Germany[a]
"Bioeconomy is the knowledge-based production and use of regenerative resources—to supply products, processes, and services in all sectors of the economy, within the context of a future-capable economic system. To achieve sustainable economic growth, bioeconomy resorts to two fundamental principles: it is based on sustainably produced, renewable natural resources and on bio-based innovations" (German Bioeconomy Council, 2018).

Japan[a]
Bioindustry in Japan refers to the health and medical sector, environmental technologies, agriculture, fisheries, and food processing (German Bioeconomy Council, 2018).

Malaysia
"Bioeconomy refers to all economic activity that is derived from the continued commercial application of biotechnology. It encompasses the production of renewable biological resources and their conversion into food, feed, chemicals, energy, and health care wellness products via innovative and efficient technologies" (Arujanan and Singaram, 2018).

Organisation for Economic Co-operation and Development (OECD)
"Bioeconomy is the set of economic activities in which biotechnology contributes centrally to primary production and industry, especially where the advanced life sciences are applied to the conversion of biomass into materials, chemicals, and fuels" (OECD, 2018).

South Africa
"The term 'bioeconomy' encompasses biotechnological activities and processes that translate into economic outputs, particularly those with industrial application. Within the South African context, these may include, but are not limited to, technological and nontechnological exploitation of natural resources such as animals, plant biodiversity, micro-organisms, and minerals to improve human health, address food security, and subsequently contribute to economic growth and improved quality of life" (Bracco et al., 2018).

United Kingdom
"The bioeconomy encompasses all economic activity derived from bio-based products and processes which contributes to sustainable and resource-efficient solutions to the challenges faced in food, chemicals, materials, energy production, health, and environmental protection. The bioeconomy is not about just one industry sector or looking at a particular scientific innovation, but encompasses the economic process" (BBSRC, n.d.).

United States
"A bioeconomy is one based on the use of research and innovation in the biological sciences to create economic activity and public benefit" (U.S. OSTP, 2012).

"The bioeconomy represents the infrastructure, innovation, products, technology, and data derived from biologically-related processes and science that drive economic growth, improve public health, agricultural, and security benefits" (U.S. OSTP, 2019).

[a]New bioeconomy strategies have been released in the native languages of these countries. The English translation is currently unavailable.

processes, and the development of new commercial products through biomanufacturing.
- The bioresource vision involves the conversion of biomass and biological materials (e.g., crops, trees) into sources of power and/or new products, such as bioplastics or biofuels.
- The bioecology vision "highlights the importance of ecological processes that optimize the use of energy and nutrients, promote biodiversity, and avoid monocultures and soil degradation" (Bugge et al., 2016, p. 1). Among biodiversity-rich countries, the bioecology vision emphasizes conservation of biological diversity and promotion of ecosystem services. Here, a country's natural endowments of biological diversity may provide raw materials or blueprints for pharmaceutical prospecting (Barbier and Aylward, 1996; Ivshina and Kuyukina, 2018; Perrings et al., 2009; Sasson and Malpica, 2018; Sedjo, 2016; Simpson et al., 1996; Trigo et al., 2013; Valli et al., 2018).

These three visions are discussed in further detail below.

Biotechnology Vision

Under the biotechnology vision, recent advances in biotechnology are prominent aspects of the bioeconomy, as exemplified in the National Bioeconomy Blueprint of the United States (Carlson, 2016; U.S. OSTP, 2012). With the release of the Blueprint in 2012, the United States became the first country to describe biotechnology as a key driver of the bioeconomy. After a long period of countries formulating new bioeconomy strategies that did not feature biotechnology, over the past year new "biotechnology" bioeconomy strategies have been released by Canada (Bioindustrial Innovation Canada, 2018), Germany (Federal Ministry of Education and Research and Federal Ministry of Food and Agriculture, 2020), Japan (Japan's General Council for Science and Technology Innovation, 2019), and the United Kingdom (HM Government, 2019). Biotechnology is seen today as a new area of technological and economic competition (BioteCanada, 2009; Gronvall, 2017; Langeveld, 2015; Li et al., 2006; Meyer, 2017; U.S. OSTP, 2012).

The approach to defining the bioeconomy under the biotechnology vision is example driven, highlighting specific production processes or products. A challenge of this technology-based definition approach is that many of the novel technologies or products involved have been deployed in more traditional economic sectors, such as agriculture and forestry. This raises questions about whether to focus the definition on the inclusion of newer applications, such as GM crop varieties, or to consider all crop

and forest production as part of the bioeconomy. For example, studies by Li and colleagues (2006) (of China), Lee (2016) (of China, India, Japan, Korea, Malaysia, and Taiwan), Carlson (2016), Trigo and colleagues (2013) (of Latin America), and the Organisation for Economic Co-operation and Development (OECD, 2018), along with the U.S. National Bioeconomy Blueprint (U.S. OSTP, 2012), consider the diffusion of GM crops as a performance indicator of the bioeconomy. In contrast, EU countries tend to consider all crops as part of the bioeconomy, with no special tracking or consideration of GM crops. This approach could be related, in part, to the fact that the growing of GM foods is banned in many individual EU countries (GMO Answers, n.d.).

Countries vary in their approach to health fields. While most definitions consider biobased pharmaceuticals to be part of the bioeconomy, the United States and China focus on a wider set of medical applications. For China, Li and colleagues (2006) emphasize not only (human and animal) vaccines, but also genome sequencing, gene therapies, tissue-engineering products, and health immunological diagnosis. In this respect, this definition mirrors many of the applications discussed in the U.S. National Bioeconomy Blueprint (U.S. OSTP, 2012). Finland and Nordic countries emphasize nutraceuticals and functional foods designed to promote health (Dubois and Gomez San Juan, 2016).

Countries also vary in their emphasis on measuring biotechnology-related research and development (R&D) activity and applications, with Canada, China, and the United States giving it greater emphasis (BioteCanada, 2009; Carlson, 2016; Li et al., 2006; U.S. OSTP, 2012). Generally, European countries deemphasize biotechnology R&D, with notable exceptions being studies from Germany (Ehrenfeld and Kropfhäußer, 2017) and Sweden (Statistics Sweden, 2018). Some studies have also included bioleaching applications in the mining industry as part of the bioeconomy (Juma and Konde, 2001; Li et al., 2006; Matyushenko et al., 2016; Pellerin and Taylor, 2008).

Bioresource Vision

The bioresource vision of the bioeconomy focuses on substitution for the fossil fuel–based production of electricity, fuel, and chemical manufacturing. A key goal is the development of new value chains for traditional biological resource–based industries (Bugge et al., 2016). Countries consistently include such activities in their definitions of and strategies for the bioeconomy. Countries, however, differ in terms of the emphasis they place on climate change mitigation, meeting Sustainable Development Goals (SDGs), energy security, and rural economic development as motivations for bioresource substitution (Bracco et al., 2018; Bugge et al., 2016; Dietz et al., 2018; Dubois and Gomez San Juan, 2016; Wreford et al., 2019).

U.S. agencies do not have a consistent set of technologies or economic activities to include in biobased production. The 2015 BioPreferred report to Congress of the U.S. Department of Agriculture (USDA) (Golden et al., 2015) evaluates seven biobased product industries contributing to the U.S. economy: agriculture and forestry, biorefining, biobased chemicals, enzymes, bioplastic bottles and packaging, forest products, and natural-fiber textiles. It excludes agriculture for food, feed, or biofuels production, as well as pharmaceuticals. New forms of biobased manufacturing (such as biobased manufactured products) accounted for only 8 percent of direct value added (value added summed over all industries equals national gross domestic product [GDP]) from biobased production. Logging, timber, and wood products accounted for 81 percent of value added, while cotton production and cotton-based textiles and apparel contributed 11 percent. In contrast, the U.S. Department of Energy's (DOE's) Billion-Ton report (Brandt et al., 2016), which focuses on bioresource supply potential, considers a broader array of technologies and products, including biobased chemicals, ethanol, biodiesel, anaerobic digestion, woody biomass and wood waste, and landfill gas.

Bioecology Vision

The bioecology vision of the bioeconomy emphasizes "the importance of ecological processes that optimize the use of energy and nutrients, promote biodiversity, and avoid monocultures and soil degradation" (Bugge et al., 2016). Recycling and reuse of biological (and other resources) is also emphasized. In this respect, the bioecology vision of the bioeconomy shares features of the circular economy. EU economic policies are increasingly focused on a circular economy concept whereby use of resources is maximized and waste is minimized, instead of a "linear economy," in which "take," "make," and "dispose" are primary elements. A circular economy employs a regenerative approach that includes design for longevity, reuse, repair, and recycling as foundational elements. Scholars have argued that the circular economy and bioeconomy represent distinct but complementary practices (Carus and Dammer, 2018; Wesseler and von Braun, 2017), with the bioeconomy placing greater emphasis on the role of biological science and processes, while certain biobased energy production and consumption are considered external to the circular economy (Carus and Dammer, 2018).

Not surprisingly, the term "circular bioeconomy" has gained traction in the European Union, and policies are being developed to maximize the use of biobased resources regarded as wastes (such as agriculture and forestry residues), with the long-term objective of gradually replacing fossil-based production with biobased (Philp and Winickoff, 2018; Reime

et al., 2016). A move toward a circular economy, particularly one with an increased use of biobased wastes, would further entangle disparate sectors for those attempting to assess or define the bioeconomy.

Biodiversity, commonly defined as the variety of living organisms within their natural environments, is relevant to understanding the bioeconomy in several contexts. First, the richness of biodiversity provides for a healthy and sustainable planet for life on Earth. Second, the traditional means of leveraging inherent biodiversity has benefits and economic value. Half the yield gains in U.S. field crops since the 1930s have been attributed to genetic improvements, including those harnessing biodiversity through crossbreeding (Huffman and Evenson, 1993). Natural products, derived from plants and animals, remain a basic source of many pharmaceuticals and agrochemicals such as insecticides. Soejarto and Farnsworth (1989) estimate that roughly one-quarter of prescription drugs contain some natural products, and this percentage increases when one considers traditional medicines used in developing countries (Simpson et al., 1996). The molecular structures of natural products also serve as blueprints for or as leads in the development of compounds (Frisvold and Day, 2008; Mateo et al., 2001). In addition to pharmaceuticals, the array of chemical structures provided by natural products has acted as a starting point for many novel herbicides, fungicides, and insecticides (Sparks et al., 2016). Third, the ability to mine and manipulate biodiversity through metabolic engineering and synthetic biology is fueling components of a purposeful bioeconomy that could be regarded as creating a novel, "digital" or "synthetic" realm of biodiversity in the form of biological tools and marketable products.

Biodiversity can be thought of as a rich, indirect resource that feeds into all components of the bioeconomy. Conversely, a loss of biodiversity could represent costs in the form of missed or unrealized opportunities for the bioeconomy. Most U.S. agricultural crops are monocultures. The practice of growing single varieties of crops can increase vulnerability to pests and pathogens and diminish services provided by a flourishing ecosystem. Proponents of the bioecological vision of the bioeconomy often stress the need for diversity with respect to which crops are grown, how crops are grown, and their genetic composition (Bugge et al., 2016).

Traditionally, biodiversity has been leveraged for benefits in different ways across numerous sectors. Desired agricultural traits depend on selection from broad genetic diversity within a species. This diversity is important in the identification of desirable genetic traits that are used and selected for in marker-assisted breeding programs, a process in which genetic sequences guide the agricultural selection process. More recently, the tools of synthetic biology and biotechnology have been applied to convert biodiversity both within and across species to a demonstrable level of direct economic benefit.

Genomic sequencing of a diversity of living organisms enables the identification of genes that could be employed in the creation of genetic pathways and circuits, using metabolic engineering to create high-value compounds. What can be created is limited only by the diversity of pathways that can be discovered. While it is likely that the bulk of the potential of biodiversity remains undiscovered, industry exploration of the biodiversity space began in earnest with the discovery of natural-product pharmaceuticals, and has continued in recent years (Gepts, 2004; Naman et al., n.d.). For example, the recently initiated Earth BioGenome Project (EBP) seeks to sequence, catalog, and characterize the genomes of Earth's eukaryotic biodiversity over a 10-year period (Lewin et al., 2018).

Reconciling Visions of the Bioeconomy

The above three different visions of the bioeconomy are not necessarily mutually exclusive. Countries formalizing bioeconomy strategies almost uniformly emphasize the substitution of biological resources for fossil fuel–based production (fundamental to the bioresource vision). Many (e.g., Canada, China, Germany, Latin America, Malaysia, the United Kingdom, the United States) simultaneously emphasize the role of biotechnology (Arujanan and Singaram, 2018; Carlson, 2016; Li et al., 2006; Trigo et al., 2013). In contrast, some applications of the bioecology vision explicitly reject GM crops as part of the bioeconomy (Bugge et al., 2016).

While different countries and studies may place a different emphasis on these three visions, there are cases in which one can find examples of all three. For example, the United States has produced several documents emphasizing different visions. The National Bioeconomy Blueprint, with its emphasis on biotechnology and health applications, corresponds most closely to the biotechnology vision (U.S. OSTP, 2012). The 2015 USDA BioPreferred report to Congress (Golden et al., 2015) and DOE's Billion-Ton report (Brandt et al., 2016), by emphasizing substitution of renewable biological resources for fossil fuels, correspond more closely to the bioresource vision. Lastly, by informing research issues such as risks to biodiversity from climate change, the EBP (Lewin et al., 2018) corresponds to the bioecology vision.

Defining the Bioeconomy Landscape

Attempts to assess the contribution of the bioeconomy and develop performance metrics for bioeconomy strategies invariably lead to decisions about which economic activities to include and exclude as direct bioeconomy components (i.e., how the landscape of the bioeconomy is defined). Such categorization is an intermediate step before the contribution of the bioeconomy

to the total economy of a country or region is measured (see Chapter 3 for discussion of measurement issues). As with the varying conceptual definitions of the bioeconomy around the world, there is no consensus across countries, or even country ministries or academic practitioners, concerning the bioeconomy landscape or how to measure it.

Because the bioeconomy is not encompassed in a discrete set of economic sectors but spans multiple sectors, developing a landscape definition is challenging. Yet, most attempts at least have a common starting point. First, certain sectors are considered wholly within (e.g., biotechnology R&D) or outside of (e.g., steel manufacturing) the bioeconomy. What remains is a set of "mixed" (Ronzon et al., 2017), "partly included" (Lier et al., 2018), or "hybrid" (Ronzon and M'Barek, 2018) sectors. For example, the production of soy printer ink (part of the larger printing ink manufacturing industry) would be part of the bioeconomy, as would bioplastics (part of a large plastics manufacturing industry).

International Approaches

Distinct differences in defining the bioeconomy landscape are seen between North American studies and those done for EU countries and Japan. Whereas Box 2-1 reviews differences among definitions of the bioeconomy in different countries, Table 2-1 illustrates the diversity of various approaches to outlining a landscape reflective of these definitions or approaches to measurement, although it is not meant to be exhaustive. This table highlights a number of academic and third-party approaches, including several used to study the U.S. bioeconomy. The final column in the table lays out the landscape outlined by this report (discussed in detail below).

EU studies tend to use a relatively broad definition of the bioeconomy landscape, including sectors in their entirety that produce or fundamentally rely on biologically produced materials. For example, not only are primary sectors (other than mining) included, but also food, beverage, tobacco, and wood products manufacturing. Although EU ministries have identified research and innovation as a key indicator, biotechnology R&D is often excluded from the bioeconomy landscape in EU countries (Ehrenfeld and Kropfhäußer, 2017). In the United States and Canada, there has been greater emphasis on applications of biotechnology, biological R&D, and substitution of biobased for fossil fuel–based products in manufacturing within traditional sectors. Primary sectors (agriculture, forestry, and fisheries) are largely excluded from the bioeconomy, with the exception of GM crops and crops grown for energy production (Carlson, 2016).

Lier and colleagues (2018) conducted a survey of ministries from EU member states tasked with monitoring the performance of the

TABLE 2-1 Sectors Included, Excluded, or Partially Included in the Bioeconomy in Selected Studies

Industry	Study Authors/Region												
	Daystar et al., 2018/U.S.	Ernst and Young, 2000/U.S.	Carlson, 2014/U.S.	de Avillez, 2011/Canada	Pellerin and Taylor, 2008/ Canada	Hevesi and Bleiwas, 2005/ New York	Ehrenfeld and Kropfhäußer, 2017/Saxony	Ronzon et al., 2017/EU	Loizou et al., 2019/Poland	Natural Resources Institute Finland, 2019/Finland	Wen et al., 2019/Japan	Causapé, 2017/EU	Smeets et al., 2013/EU	Philippidis et al., 2014/EU	**NASEM/U.S.**
Crop production	+	—	+	+	+	—	+	++	++	++	++	++	++	++	**+**
Livestock production	—	—	—	+	—	—	+	++	++	++	++	++	++	++	**E**
Fisheries/aquaculture	—	—	—	+	—	—	+	++	++	++	++	++	++	++	**E**
Forestry	++	—	—	+	—	—	+	++	++	++	++	++	++	++	**E**
Electricity generation	—	—	—	+	—	—	+	+	—	+	+	+	+	+	**+**
Mining (bioleaching)	—	—	—	—	+	—	—	—	—	—	—	—	—	—	**E**
Processed food	+	—	+	+	+	—	+	++	++	+	++	++	++	++	**+**
Beverages and tobacco	—	—	—	+	+	—	—	++	++		++	++	++	++	—
Leather and products	—	—	—		—	—	—	++	++	+	—	—	++	++	—
Wood manufacturing	++	—	—	+	—	—	+	++	++	+	++	+	++	++	—
Paper products	+	—	—	+	+	—	—	++	++	+	++	—	++	++	—

Furniture manufacturing	+	—	—	—	—	—	—	+	+	+	—	—	—	—	—
Textiles	+	—	—	+	—	—	—	+	+	+	—	+	++	++	E
Apparel	+	—	—	—	—	—	—	+	+	+	—	—	—	++	—
Pharmaceuticals	—	+	+	++	++	+	+	+	+	++	—	—	+	—	++
Chemicals	+	—	+	+	+	—	+	+	+	+	—	+	+	+	+
Plastics and rubber	+	—	+	—	—	—	—	+	+	+	—	—	+	—	+
Biotechnology R&D	—	++	++	++	—	++	+	—	—	—	—	—	—	—	++
Other physical, engineering, and life sciences R&D	—	+	+	+	—	+	+	—	—	—	—	—	—	—	+
Medical diagnostics	—	—	—	+	—	—	—	—	—	—	—	—	—	—	++
Health care	—	—	—	+	+	—	—	—	—	—	—	—	—	—	—
Druggists' goods (wholesalers)	—	—	—	+	—	—	—	—	—	—	—	—	—	—	—
Agriculture supplies (wholesale)	—	—	—	+	—	—	—	—	—	—	—	—	—	—	—
Construction	—	—	—	—	—	—	—	—	—	+	—	—	+	—	—
Water treatment and supply	—	—	—	—	—	—	—	—	—	+	—	—	—	—	—
Nature tourism, hunting, fishing	—	—	—	—	—	—	—	—	—	+	—	—	—	—	—

NOTES: + = a sector in which some activities are included; ++ = a sector that is wholly included; E = an emerging sector in which some commercial-scale applications are anticipated in the near future. Blank cells represent industries not included in the bioeconomy at all.

bioeconomy or developing bioeconomy strategies. Respondents were asked which activities were completely included, partly included, or not included in the bioeconomy sector (see Table 2-2). Combining results from responding countries, 15 different industries were identified, although not all countries included the same industries. Only 3 of the 15 industries were listed as completely included in the bioeconomy by all respondents: agriculture, the food industry, and forestry. For the other 12 industries, countries differed on their level of inclusion. Most, but not all, countries included aquaculture, fisheries, wood products manufacturing, and pulp and paper manufacturing as wholly in the bioeconomy. Some ministries also included hunting, nature-based tourism and recreation, transportation of biobased products, and even some construction activities as either wholly or partly in the bioeconomy, as there was even less agreement here.

Although not treated as an economic activity or sector, most ministries identified "investment in research and innovation" as a key indicator of performance for their bioeconomy (Lier et al., 2018). This is different from the approach taken by Sweden, which explicitly includes research and experimental development in biotechnology as a sector as part of the bioeconomy (Statistics Sweden, 2018). Similarly, Ehrenfeld and Kropfhäußer (2017) found that 18 percent of firms within the Central German bioeconomy were categorized under scientific R&D industry codes.

Trade-offs are involved in adopting narrower versus broader definitions of what activities are included in the bioeconomy. If one adopts a broad, highly inclusive definition, the bioeconomy is dominated by mature economic activities (e.g., manufacturing of wood furniture) that (as yet) involve neither applications of biological research or biotechnology nor the substitution of biological for petrochemical resources. Adopting a broader definition has the advantage of including the totality of such sectors as agriculture, forestry, wood manufacturing, and food processing. These sectors are already characterized and defined in national income accounts and recorded regularly in government statistics. This facilitates measurement, but measures of the bioeconomy heavily weighted toward such mature sectors may indicate that the bioeconomy is a shrinking share of economic activity, incomes, and wages over time.

In contrast, a narrower definition, based more on biological innovations, may be better equipped to track innovation and dynamism within mature sectors. For example, under a narrower definition of the bioeconomy, forestry may not be included. Yet, as adoption of future biotechnology applications (NASEM, 2019) progresses, activities within the forestry sector would increasingly be included in the bioeconomy. Likewise, innovations in cellular agriculture could bring more activities within livestock production or food processing under the umbrella of the bioeconomy.

TABLE 2-2 Results of a Survey of European Union Ministries on Which Industries Are Included, Partly Included, and Not Included in the Bioeconomy Sector at the National Level

Industry	Denmark	Estonia	Finland	France	Germany	Italy	Latvia	Netherlands	Norway	Slovakia	Spain	Turkey
Agriculture	++	++	++	++	++	++	++	++	++	++	++	++
Food industry	++	++	++	++	++	++	++	++	++	++	++	++
Forestry	++	++	++	++	++	++	++	++	++	++	++	++
Aquaculture	++	++	++	++	++	++	++	+	++	+	++	++
Fisheries	++	++	++	++	++	++	++	+	++	+	++	++
Pulp and paper	++	++	++	++	++	++	—	++	++	+	++	++
Renewable energy	+	++	++	+	+	++	++	++	++	++	++	++
Wood products	++	++	++	++	++	++	++	+	++	+	++	+
Chemical industry	+	+	++	+	+	++	+	+	+	+	++	++
Pharmaceutical industry	+	+	++	+	+	++	+	++	+	+	+	++
Water supply	+	—	++	+	+	+	++	++	++	+	+	++
Hunting	+	++	++	—	+	—	++	—	++	+	—	++
Transportation of biobased products	+	++	++	++	+	—	—	+	+	—	++	—
Nature tourism/recreation	+	++	++	+	—	—	+	—	+	—	+	++
Construction	+	—	++	+	+	—	+	—	+	—	+	++

NOTES: + = a sector in which some activities are included; ++ = a sector that is wholly included. Blank cells represent industries not included in the bioeconomy at all.
SOURCE: Lier et al., 2018.

Yet, if one adopts too narrow a definition of what to include in the bioeconomy, it becomes more difficult to anticipate changes brought about by scientific discovery and technological innovation, which in turn makes it more difficult to track the growth and performance of the bioeconomy in consistent ways over time. For example, advances in biological innovations and biological applications of informatics are leading to rapid technological change in agriculture. Thus, decisions concerning what is included in or excluded from the bioeconomy will need to be determined and adapted regularly. This will create challenges for data collection, measurement, and tracking of bioeconomy performance across countries and over time.

Moreover, the third element of the committee's Statement of Task was to "outline metrics commonly used to identify strategic leadership positions in the global economy and identify areas in which the US currently maintains leadership positions and is most competitive." Defining the bioeconomy too narrowly could make international comparisons of bioeconomy performance more difficult as other countries harmonized toward broader definitions of and metrics for bioeconomy performance. For example, extensive efforts are under way to develop harmonized measures of the bioeconomy among EU countries (Bracco et al., 2018; EC, 2018; Parisi and Ronzon, 2016). As discussed above, EU countries tend to include more entire economic sectors in their definitions of the bioeconomy relative to North America. Data on these aggregate sectors are collected in a common way across countries. It would therefore be possible (though nontrivial) to construct measures of the U.S. bioeconomy that would be comparable to those being developed by other countries. Quantitative measurement issues are discussed in detail in Chapter 3.

DEFINING THE BIOECONOMY LANDSCAPE IN THE UNITED STATES

As discussed in Chapter 1, the committee has adopted the following definition of the U.S. bioeconomy:

> ***The U.S. bioeconomy is economic activity that is driven by research and innovation in the life sciences and biotechnology, and that is enabled by technological advances in engineering and in computing and information sciences.***[1]

This definition encompasses all products, processes, and services that interact with or are built specifically for "research and innovation in the life

[1]For the purposes of this report, the term "life sciences" is intended to include the biological, biomedical, environmental biology, and agricultural sciences.

sciences and biotechnology." It is intended to be flexible enough to anticipate the inclusion of new advances and applications within the life sciences and all of biotechnology, such as the use of clustered regularly interspaced short palindromic repeats (CRISPR) technology for genome editing or developments in cellular agriculture. Additionally, the committee's definition references the impacts other disciplines have had on the life sciences. As explored in Chapter 1, the fields of engineering have enabled high-throughput experimentation, while the computing and information sciences have greatly enabled the collection, analysis, sharing, and storage of biological information. These enabling technologies have changed the face of research in the life sciences and will continue to open up new avenues for R&D.

The emphasis this definition places on biotechnology is reflected in Table 2-1 and Figure 2-2, as all biotechnology R&D is included in the landscape laid out by this report's definition. Additionally, the table includes Es representing sectors with emerging applications that are currently in the R&D phase but have potential for commercial application in the near future. As these applications continue to develop, there will be a need for continual reassessment of whether new and emerging fields, or existing fields undergoing technological advancement, belong in the bioeconomy. An example is forestry, which currently would not be included in the U.S. bioeconomy based on the fact that the extent to which biotechnology or the use of produced biomass for fermentation is used in relation to the industry in the United States is not thought to be significant at this point. However, a recent report of the National Academies (NASEM, 2019) lays out a potential future for the use of biotechnology in promoting and protecting forest health, which would therefore make forestry an important contributor to the bioeconomy.

A number of new and exciting products and biotechnologies, all of which would be included in the above definition of the bioeconomy, are outlined in both the National Academies' report *Preparing for Future Products of Biotechnology* (NASEM, 2017) and the Engineering Biology Research Consortium report *Engineering Biology* (2019). Examples of biotechnology products (and the companies that produced them) that fall within the bioeconomy include platform technologies for creating engineered strains of microorganisms designed to perform specific biosynthetic functions (CB Insights, 2017; Kunjapur, 2015); microorganisms developed to clean up the environment by recycling metal or acting as environmental biosensors; clothing made from biosynthetic spider silk (Kunjapur, 2015); and meat alternatives made with biosynthetic protein additives from yeast, such as the hemoglobin used to add a "meaty" flavor (Brodwin and Bendix, 2019). To further clarify how the above definition informs the bioeconomy landscape, material examples from different sectors, and the rationale for their inclusion, are presented below.

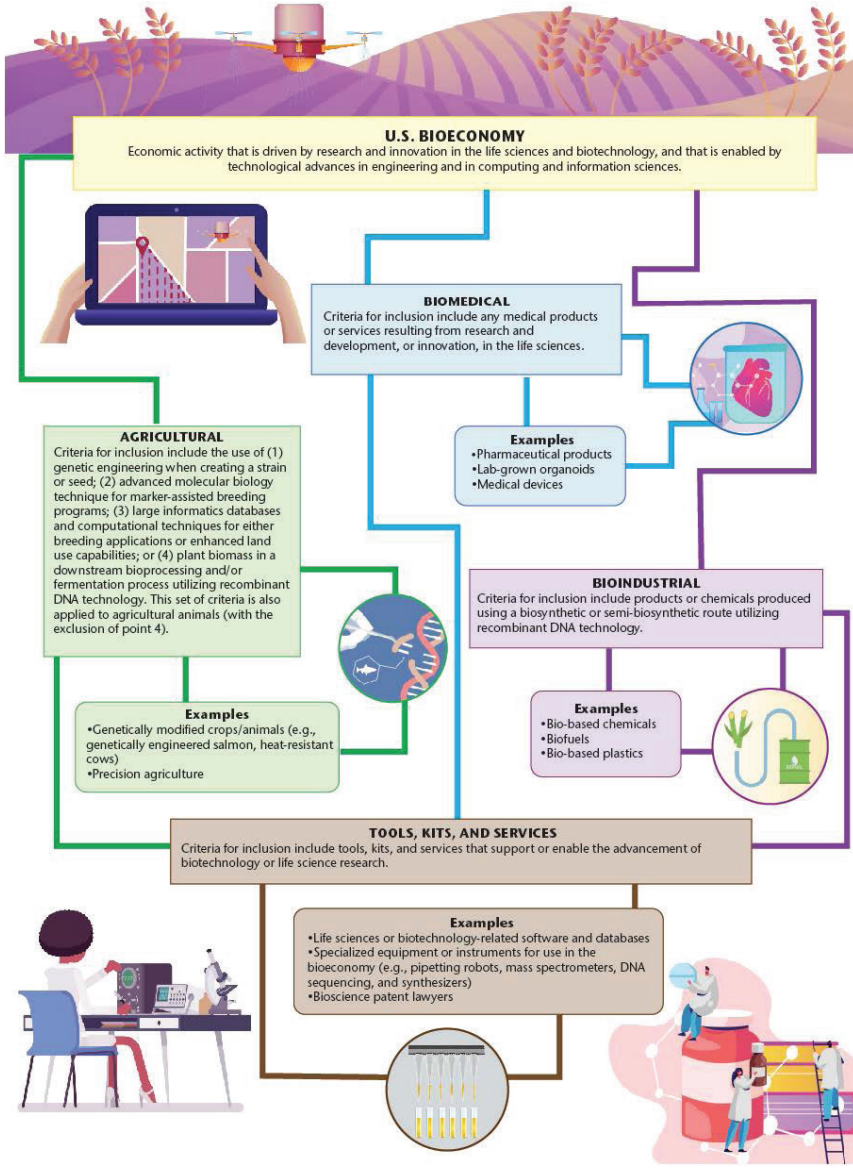


FIGURE 2-2 Examples and explanations of highlighted sectors of the bioeconomy landscape that fall under the definition put forth in this report.

Agricultural Area

According to the committee's definition, the U.S. bioeconomy includes most crops, because many crops grown in the United States interact with biotechnology or research in the life sciences during their life cycle. The committee identified four main criteria for inclusion within the agriculture sector: (1) the use of genetic engineering when creating a strain or seed, (2) the use of advanced molecular biology techniques for marker-assisted breeding programs, (3) the use of large informatics databases and computational techniques for either breeding applications or enhanced land-use capabilities (i.e., precision agriculture), or (4) the use of plant biomass in a downstream bioprocessing and/or fermentation process utilizing recombinant and synthetic DNA technologies. The computational approaches mentioned in the third of these criteria include breeding capabilities such as accelerated breeding techniques and examination of genomes to plan genetic crosses. Additionally, computational techniques can enhance land use when drone or artificial intelligence technologies are used to help with everything from water management to weed and pest scouting. The committee would exclude any crop varieties that do not meet these four criteria from its assessment of the U.S. bioeconomy.

The committee also applies the first three of these criteria for agricultural animals. In March 2019, the United States gave approval to AquaBounty, a biotech company that grows GM salmon, to start growing and selling those fish in the United States (Bloch, 2019). Already approved and sold in Canada, AquaBounty salmon are enhanced to grow at twice the rate with half the nutritional requirements of normal salmon, with no loss in nutritional value to the consumer (Bloch, 2019). While products from genetically engineered land animals have not hit the U.S. market, a great deal of research has focused on engineering desirable traits into animals and insects. For example, researchers have engineered cattle that are heat-resistant to help them survive in warmer climates (Ledford, 2019), as well as cattle that are "polled" (meaning without horns), making it safer for both their human handlers and the cattle themselves, as the process of dehorning is painful and dangerous (Akst, 2016). Insects are being developed as both a food source and a means of pest control. Examples include a company using farmed insects for protein in products such as pet food (Burwood-Taylor, 2019) and a genetically engineered moth used for pest control for cabbage (Zhang, 2017). These products are included in the bioeconomy, and will start to make larger economic contributions as they clear regulatory hurdles.

Additional examples of animal products included in the bioeconomy include "lab-grown meats," also known as "cellular agriculture." While not the same as a classic "meat alternative," "lab-grown" meat is "the use of animal cell culture technology to grow animal tissue directly from animal cells, rather than from a live animal" (Saavoss, 2019). This is a process by which

muscle cells are cultured from biopsies to produce the exact composition of animal meat without the need for animal husbandry—another example of meat that relies heavily on new biotechnologies and would therefore be included in the bioeconomy.

Biomedical Area

Any medical products or services resulting from R&D, or innovation, in the life sciences fit within the committee's definition of the bioeconomy. All pharmaceuticals require R&D before being approved and allowed onto the market. The research required to produce a final product frequently includes the drug discovery paradigm of using biological information and processes to obtain an initial product that is iteratively tested, screened for safety and efficacy, and produced at scale. Increasingly, engineering approaches are used to identify a starting drug molecule. These processes include automated screening of large chemical libraries to identify a starting drug molecule and in silico screening of molecules in the binding regions of important protein targets. All of these steps require "research and innovation in the life sciences," meaning all pharmaceutical products, and the processes used in their discovery, are included in the bioeconomy.

The use of biological R&D is equally important for the creation of medical devices. Some medical devices require the extensive use of newly developed biotechnologies and the most current biological research. For example, there are many iterations of the brain-controlled robotic arm, including a new version that does not require invasive surgery but instead uses a noninvasive brain–computer interface (Durham, 2019). Other devices under development—such as cell-based biosensors for diagnosis and lab-grown organoids—rely heavily on advances in human biology. Because all medical devices have life science R&D in their life cycle, their inclusion in the bioeconomy is warranted.

Bioindustrial Area

As with the downstream fermentation processes in agriculture, any product or chemical produced using a biosynthetic or semibiosynthetic route utilizing recombinant DNA technology is included in the bioeconomy. However, any chemical manufactured through strictly chemical synthesis is excluded under this definition. An example that highlights the biosynthetic versus chemically synthetic processes for producing a chemical is the common industrial additive 1,3-propanediol. Using GM bacteria to convert a sugar-based starting product into the desired chemical (Biebl et al., 1999), this product can be produced at large scale for a number of common fiber applications, such as added durability for carpets and rugs (DuPont Tate and Lyle

BioProducts, 2006). This example illustrates a chemical previously produced through chemical synthesis that is now being produced primarily through a biosynthetic process. Currently, it is difficult to parse out what fraction of the total production of a manufactured chemical is made through a fermentation versus a chemical synthesis process, making it challenging to measure the contribution of certain chemicals to the bioeconomy.

Cross-Cutting Tools, Kits, and Services

Any tool, kit, or service that supports or enables the advancement of biotechnology or life sciences research is included in the U.S. bioeconomy landscape, with the recognition that it can be difficult to decouple tools or services that function both within and outside the defined parameters of the bioeconomy. A clear example of a supporting tool is any software used specifically in life sciences laboratories. Software such as SnapGene, which is used to view and analyze genetic sequences, would be included because it is a computing technology that functions primarily to advance research in the life sciences. In contrast, standard word processing software, while still useful in a scientific setting, would be excluded because of its wide range of other uses. Another tool with examples both within and outside of the bioeconomy is datasets and databases. The number and size of datasets have continually increased as the technologies for acquiring data have advanced. This makes life science–specific datasets, such as databases of genomic sequences, a valuable component of the bioeconomy (as discussed further in Chapters 5 and 7).

Life sciences–specific instrumentation, such as pipetting robots, is also included in the bioeconomy. Other instrumentation important across all bioeconomy sectors is DNA sequencing and synthesis technologies. Many of the products and services described in this landscape rely on the ability to sequence and synthesize DNA with increasing speed and at increasingly lower costs (NASEM, 2017; also discussed in more detail in Chapter 5). It is important to note that some instruments, such as mass spectrometers, are critical to the bioeconomy while also serving scientific purposes that are completely outside the scope of the bioeconomy. Mass spectrometers are the workhorse instruments in the field of proteomics, an important field of life science. Additionally, the instruments are critical to the field of chemistry in helping with many tasks, including the analysis and identification of small-molecule products. Because of these differing functions, parsing out the economic contributions of mass spectrometers to the bioeconomy becomes difficult.

In addition to various tools and instrumentation, any services that exist to advance biotechnology and the life sciences are included in the scope of the bioeconomy. Examples include the bioscience patent lawyers

that help move new biotechnologies through the complex system of patent laws (Carlson, 2014). Bioscience patent lawyers provide an expertise that is specific to the bioeconomy by understanding both patent law and the biotechnologies they are guiding through the patent process. The specificity of their expertise differentiates the services of these lawyers from other, more general services that are also important to biotechnology and the life sciences but require no biotechnology-specific knowledge or training. These lawyers are included in the bioeconomy because they provide an indispensable service that directly and specifically helps move new biotechnologies onto the economic market.

Moving Forward in Defining the Landscape

As discussed in relation to specific products, it can be difficult to measure the economic activity related to the bioeconomy for products that have multiple uses. At high levels of aggregation used to report U.S. GDP, several U.S. sectors would be treated as mixed or hybrid sectors, with some activities within and others outside the bioeconomy: agriculture (GM crops); utilities (biomass electricity); food and beverage and tobacco products (bioengineered products); chemical products (pharmaceuticals, biobased chemical products); plastics and rubber products (e.g., bioplastics); professional, scientific, and technical services (biotechnology R&D); and ambulatory health care services (e.g., certain medical laboratory services).

At finer scales of sector definition than those used to report GDP, industries are classified in the United States, Canada, and Mexico in terms of North American Industry Classification System (NAICS) codes and in the European Union according to Nomenclature générale des Activités économiques dans les Communautés Européennes codes. The process of defining the bioeconomy landscape (whereby sectors are excluded, wholly included, or partially included in the bioeconomy) can be repeated at this finer scale. For example, R&D in biotechnology (NAICS 541714) or biomass electric power generation (NAICS 221117) would be considered within the bioeconomy, while printing ink manufacturing (NAICS 325910) would be a mixed sector, with soy ink production being included in the bioeconomy.

Even at finer scales of definition, many sectors of the U.S. economy will still be mixed (i.e., only some activities included in the bioeconomy). A common approach for addressing this is to conduct industry surveys to determine which type of production within a sector may be "biobased" (e.g., Golden et al., 2015; Ronzon et al., 2017; Wierny et al., 2015). For example, plastics manufacturers might be surveyed to determine how much of their employment and production is devoted to bioplastics, and this subset of bioplastic production would then be included in the bioeconomy. Another approach would be to seek changes in the definition of NAICS codes to

better capture bioeconomy activity (see Chapter 3 for further discussion of NAICS codes).

CONCLUSIONS

This chapter has reviewed the history of the study of the bioeconomy as a topic of research. It has highlighted the variety of approaches taken by scholars and governments in defining the bioeconomy as a concept. In researching and understanding definitions used by other countries and academics, as well as previous definitions used by the United States, the committee decided to take a broad approach to defining the bioeconomy while making sure to include new enabling technologies.

Conclusion 2-1: The committee has adopted the following definition: *"The U.S. bioeconomy is economic activity that is driven by research and innovation in the life sciences and biotechnology, and that is enabled by technological advances in engineering, computing, and information sciences."*

For the purposes of this report, the term "life sciences" is intended to be inclusive of the biological, biomedical, environmental biology, and agricultural sciences. The above definition is meant to be inclusive of new and emerging technologies and products in the life sciences. This chapter also has recognized the importance of wording other definitions based on the economic view of the government or group writing the definition. With this in mind, it is important to point out the differences in narrow and broad definitions of the bioeconomy.

Conclusion 2-2: Trade-offs are associated with adopting narrower versus broader definitions of what activities are to be included in the bioeconomy.

If one adopts a broad, highly inclusive definition, the bioeconomy is dominated by mature economic activities that are not driven by life science and biotechnology research and innovation or are not substituting fossil fuel–based with biological resource–based production. One must also be careful lest the definition make it more difficult to anticipate changes brought about by scientific discovery and technological innovation, which will in turn make it more difficult to track the performance of the bioeconomy in consistent ways over time.

The third part of the committee's Statement of Task was to "outline metrics commonly used to identify strategic leadership positions in the global economy and identify areas in which the U.S. currently maintains

leadership positions and is most competitive." In light of the above considerations, the committee drew the following conclusion:

Conclusion 2-3: Defining the bioeconomy too narrowly will make international comparisons of the performance of the bioeconomy more difficult, as other countries are harmonizing toward broader definitions and metrics for bioeconomy performance.

The broader definitions of other countries inform a landscape that is more inclusive and can be more easily compared across economies relative to a narrower definition. The next chapter continues to explore tools for measuring the U.S. bioeconomy, in addition to methods of comparison for leadership in the bioeconomy among different countries.

REFERENCES

Akst, J. 2016. Genetically engineered hornless dairy calves. *The Scientist*, May 10. https://www.the-scientist.com/the-nutshell/genetically-engineered-hornless-dairy-calves-33553 (accessed August 30, 2019).

Arujanan, M., and M. Singaram. 2018. The biotechnology and bioeconomy landscape in Malaysia. *New Biotechnology* 40(Pt. A):52–59. doi: 10.1016/j.nbt.2017.06.004.

Barbier, E. B., and B. A. Aylward. 1996. Capturing the pharmaceutical value of biodiversity in a developing country. *Environmental and Resource Economics* 8(2):157–181.

BBSRC (Biotechnology and Biological Sciences Research Council). n.d. *Biosciences for the future. Building the bioeconomy*. https://bbsrc.ukri.org/research/briefings/bioeconomy (accessed July 30, 2019).

Biebl, H., K. Menzel, A. P. Zeng, and W.-D. Deckwer. 1999. Microbial production of 1,3-propanediol. *Applied Microbiology and Biotechnology* 52(3):289–297. doi: 10.1007/s002530051523.

Bioindustrial Innovation Canada. 2018. *Canada's bioeconomy strategy: Leveraging our strengths for a sustainable future*. https://docs.wixstatic.com/ugd/b22338_1906a509c5c44870a6391f4bde54a7b1.pdf (accessed October 19, 2019).

BioteCanada. 2009. *The Canadian blueprint: Beyond moose & mountains. How we can build the world's leading bio-based economy*. Ottawa, Canada: BioteCanada.

Birner, R. 2018. Bioeconomy concepts. In *Bioeconomy: Shaping the transition to a sustainable, biobased economy*, edited by I. Lewandowski. Cham, Switzerland: Springer. Pp. 17–38.

Bloch, S. 2019. AquaAdvantage, the first GMO salmon, is coming to America. *The New Food Economy*, March 11. https://newfoodeconomy.org/fda-aquabounty-gmo-salmon-seafood-restriction-market (accessed August 30, 2019).

Bonny, S. 2014. Taking stock of the genetically modified seed sector worldwide: Market, stakeholders, and prices. *Food Security* 6(4):525–540.

Bracco, S., O. Calicioglu, M. Gomez San Juan, and A. Flammini. 2018. Assessing the contribution of bioeconomy to the total economy: A review of national frameworks. *Sustainability* 10(6):1698.

Brandt, C. C., M. R. Davis, B. Davison, L. M. Eaton, R. A. Efroymson, M. R. Hilliard, K. Kline, M. H. Langholtz, A. Myers, S. Shahabaddine, T. J. Theiss, A. F. Turhollow, Jr., E. Webb, I. Bonner, G. Gresham, J. R. Hess, P. Lamers, E. Searcy, K. L. Abt, M. A. Buford, D. P. Dykstra, P. D. Miles, P. Nepal, J. H. Perdue, K. E. Skog, D. W. Archer, H. S. Baumes, P. D. Cassidy, K. Novak, R. Mitchell, N. Andre, B. C. English, C. Hellwinckel, L. H. Lambert, J. McCord, T. G. Rials, R. C. Abt, B. J. Stokes, A. Wiselogel, D. Adams, B. Boykin, J. Caul, A. Gallagher, J. Largen, M. Lucas, B. Mar, A. Moulton, K. Satalino, G. Shields, V. Owens, L. R. Johnson, C. Daly, M. Halbleib, J. Rogers, R. Davis, A. Milbrandt, N. Brown, K. C. Lewis, A. Coleman, C. Drennan, M. Wigmosta, T. Volk, S. Schoenung, and W. Salverson. 2016. *2016 billion-ton report: Advancing domestic resources for a thriving bioeconomy*, *Volume 1: Economic availability of feedstocks*. ORNL/TM-2016/160. U.S. Department of Energy, Office of Energy Efficiency and Renewable Energy. doi: 10.2172/1435342.

Brodwin, E., and A. Bendix. 2019. The startup behind Silicon Valley's favorite "bleeding" veggie burger has scored a major victory in its battle for legitimacy. *Business Insider*, August 1. https://www.businessinsider.com/impossible-foods-bleeding-veggie-burger-ingredient-gets-fda-green-light-2018-7 (accessed August 30, 2019).

Bugge, M., T. Hansen, and A. Klitkou. 2016. What is the bioeconomy? A review of the literature. *Sustainability* 8(7):691. doi: 10.3390/su8070691.

Burwood-Taylor, L. 2019. French insect farming startup Ynsect raises $125M Series C breaking European agtech record. *AFN*, February 20. https://agfundernews.com/breaking-french-insect-farming-startup-ynsect-raises-125m-series-c-breaking-european-agtech-record.html (accessed August 30, 2019).

Carlson, R. 2014. How big is the bioeconomy? *Nature Biotechnology* 32:598. https://www.nature.com/articles/nbt.2966 (accessed August 30, 2019).

Carlson, R. 2016. Estimating the biotech sector's contribution to the U.S. economy. *Nature Biotechnology* 34(3):247–255. https://www.nature.com/articles/nbt.3491 (accessed August 30, 2019).

Carus, M., and L. Dammer. 2018. The circular bioeconomy—concepts, opportunities, and limitations. *Industrial Biotechnology* 14(2). doi: 10.1089/ind.2018.29121.mca.

Causapé, A. J. M., G. Philippidis, and A. I. Sanjuán López. 2017. Analysis of structural patterns in highly disaggregated bioeconomy sectors by EU Member States using SAM/IO multipliers. *JRC Technical Reports*, EUR 28591. Brussels, Belgium: Publications Office of the European Union.

CB Insights. 2017. *Grapeless wine and cowless milk: 60+ synthetic biology startups in a market map*. https://www.cbinsights.com/research/synthetic-biology-startup-market-map (accessed August 30, 2019).

D'Amato, D., N. Droste, B. Allen, M. Kettunen, K. Lähtinen, J. Korhonen, P. Leskinene, B. D. Matthies, and A. Toppinen. 2017. Green, circular, bio economy: A comparative analysis of sustainability avenues. *Journal of Cleaner Production* 168:716–734. doi: 10.1016/j.jclepro.2017.09.053.

Daystar, J., R. Handfield, J. S. Golden, E. McConnell, B. Morrison, R. Robinson, and K. Kanaoka. 2018. *An economic impact analysis of the U.S. biobased products industry.* https://www.biopreferred.gov/BPResources/files/BiobasedProductsEconomicAnalysis2018.pdf (accessed October 14, 2019).

de Avillez, R. 2011. Measuring the contribution of modern biotechnology to the Canadian economy (No. 2011-18). http://www.csls.ca/reports/csls2011-18.pdf (accessed October 19, 2019).

de Besi, M., and K. McCormick. 2015. Towards a bioeconomy in Europe: National, regional and industrial strategies. *Sustainability* 7(8):10461–10478.

Deconinck, K. 2019. New evidence on concentration in seed markets. *Global Food Security* 23:135–138. doi: 10.1016/j.gfs.2019.05.001.

Devaney, L., and M. Henchion. 2018. Consensus, caveats and conditions: International learnings for bioeconomy development. *Journal of Cleaner Production* 174:1400–1411.

Dietz, T., J. Börner, J. Förster, and J. von Braun. 2018. Governance of the bioeconomy: A global comparative study of national bioeconomy strategies. *Sustainability* 10(9):3190. doi: 10.3390/su10093190.

Dubois, O., and M. Gomez San Juan. 2016. *How sustainability is addressed in official bioeconomy strategies at international, national and regional levels: An overview*. Environment and Natural Resources Management Working Paper 63. http://www.fao.org/3/a-i5998e.pdf (accessed August 30, 2019).

DuPont Tate and Lyle BioProducts. 2006. *DuPont Tate & Lyle Bio Products begin Bio-PDO™ production in Tennessee.* http://www.duponttateandlyle.com/news_112706 (accessed October 2, 2019).

Durham, E. 2019. *First-ever noninvasive mind-controlled robotic arm.* https://engineering.cmu.edu/news-events/news/2019/06/20-he-sci-robotics.html (accessed August 30, 2019).

EC (European Commission). 2018. *Jobs and wealth in the EU bioeconomy/JRC-bioeconomics*. https://ec.europa.eu/knowledge4policy/dataset/7d7d5481-2d02-4b36-8e79-697b04fa4278_en (accessed on July 24, 2019).

Ehrenfeld, W., and F. Kropfhäußer. 2017. Plant-based bioeconomy in central Germany—a mapping of actors, industries and places. *Technology Analysis & Strategic Management* 29(5):514–527. doi: 10.1080/09537325.2016.1140135.

Engineering Biology Research Consortium. 2019. *Engineering biology: A research roadmap for the next-generation bioeconomy*. https://roadmap.ebrc.org (accessed July 3, 2019).

Enríquez, J. 1998. Genomics and the world's economy. *Science* 281(5379):925–926. doi: 10.1126/science.281.5379.925.

Ernst & Young. 2000. *The economic contributions of the biotechnology industry to the U.S. economy.* http://bei.jcu.cz/Bioeconomy%20folders/documents/bioeconomy/the-economic-contributions-of-the-biotechnology-industry-to-the-u-s-economy (accessed October 19, 2019).

Federal Ministry of Education and Research and Federal Ministry of Food and Agriculture. 2020. *National Bioeconomy Strategy—Summary.* https://www.bmbf.de/files/2020_1501_National-Bioeconomy-Strategy_Summary_accessible.pdf (accessed January 15, 2020).

Frisvold, G., and R. Day. 2008. Bioprospecting and biodiversity: What happens when discoveries are made? *Arizona Law Review* 50:545–576.

Gepts, P. 2004. Who owns biodiversity, and how should the owners be compensated? *Plant Physiology* 134:1295–1307. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC419806/pdf/pp1341295.pdf (accessed August 30, 2019).

German Bioeconomy Council. 2018. *Bioeconomy policy (part III): Update report of national strategies around the world*. https://biooekonomierat.de/fileadmin/Publikationen/berichte/GBS_2018_Bioeconomy-Strategies-around-the_World_Part-III.pdf (accessed August 30, 2019).

GMO Answers. n.d. *GMOs globally*. https://gmoanswers.com/gmos-globally (accessed August 30, 2019).

Golden, J. S., R. B. Handfield, J. Daystar, and T. E. McConnell. 2015. *An economic impact analysis of the U.S. biobased products industry: A report to the Congress of the United States of America*. https://www.biopreferred.gov/BPResources/files/EconomicReport_6_12_2015.pdf (accessed August 30, 2019).

Golembiewski, B., N. Sick, and S. Bröring. 2015. The emerging research landscape on bioeconomy: What has been done so far and what is essential from a technology and innovation management perspective? *Innovative Food Science & Emerging Technologies* 29:308–317. doi: 10.1016/j.ifset.2015.03.006.

Gronvall, G. K. 2017. Maintaining U.S. leadership in emerging biotechnologies to grow the economy of the future. *Health Security* 15(1):31–32.

Haarich, S., S. Kirchmayr-Novak, A. Fontenla, M. Toptsidou, S. Hans, and the European Commission. 2017. *Bioeconomy development in EU regions.* https://ec.europa.eu/research/bioeconomy/pdf/publications/bioeconomy_development_in_eu_regions.pdf (accessed August 30, 2019).

Healy, B. 1992a. *Investing in the bioeconomy*. Presented before the Greater Baltimore Committee and the Greater Baltimore Venture Capital Group, October 21. https://oculus.nlm.nih.gov/cgi/f/findaid/findaid-idx?c=nlmfindaid;idno=101600265;view=reslist;didno=101600265;subview=standard;focusrgn=C02;cc=nlmfindaid;byte=43814314 (accessed November 1, 2019).

Healy, B. 1992b. *NIH: The modern wonder well spring of the biological revolution biomedicine, and the bioeconomy*. Presented at the City Club Forum, May 15. https://oculus.nlm.nih.gov/cgi/f/findaid/findaid-idx?c=nlmfindaid;idno=101600265;view=reslist;didno=101600265;subview=standard;focusrgn=C02;cc=nlmfindaid;byte=43814314 (accessed November 1, 2019).

Healy, B. 1994. On light and worth: Lessons from medicine. *Vassar Quarterly* 90(4):10–13.

Hevesi, A., and K. Bleiwas. 2005. *The economic impact of the biotechnology and pharmaceutical industries in New York*. New York: Office of the State Comptroller.

HM Government. 2019. *Growing the bioeconomy. Improving lives and strengthening our economy: A national bioeconomy strategy to 2030*. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/761856/181205_BEIS_Growing_the_Bioeconomy__Web_SP_.pdf (accessed August 30, 2019).

Howard, P. H. 2015. Intellectual property and consolidation in the seed industry. *Crop Science* 55(6):2489–2495.

Huffman, W. E., and R. E. Evenson. 1993. The effects of R&D on farm size, specialization, and productivity. *Industrial Policy for Agriculture in the Global Economy* 12:41–72.

Ivshina, I. B., and M. S. Kuyukina. 2018. Specialized microbial resource centers: A driving force of the growing bioeconomy. In *Microbial resource conservation*. Cham, Switzerland: Springer. Pp. 111–139.

Japan's General Council for Science and Technology Innovation. 2019. *Bio Strategy 2019—Towards the formation of a bio-community that is sympathetic from home and abroad* (English translation). https://www.kantei.go.jp/jp/singi/tougou-innovation/pdf/biosenryaku2019.pdf (Japanese) (accessed January 31, 2020).

Juma, C., and V. Konde. 2001. *Industrial and environmental applications of biotechnology*. Geneva, Switzerland: United Nations Conference on Trade and Development.

Kunjapur, A. 2015. An introduction to start-ups in synthetic biology. *PLOS Synbio Community*, September 8. https://blogs.plos.org/synbio/2015/09/08/an-introduction-to-start-ups-in-synthetic-biology (accessed August 30, 2019).

Langeveld, J. W. A. 2015. *Results of the JRC-SCAR bioeconomy survey.* https://www.scar-swg-sbgb.eu/lw_resource/datapool/_items/item_24/survey_bioeconomy_report1501_full_text.pdf (accessed October 2, 2019).

Le Feuvre, P. 2019. *Transport biofuels—Tracking clean energy progress.* https://www.iea.org/tcep/transport/biofuels (accessed October 12, 2019).

Ledford, H. 2019. Gene-edited animal creators look beyond U.S. market. *Nature*, February 21. https://www.nature.com/articles/d41586-019-00600-4 (accessed August 30, 2019).

Lee, D. 2016. Bio-based economies in Asia: Economic analysis of development of bio-based industry in China, India, Japan, Korea, Malaysia and Taiwan. *International Journal of Hydrogen Energy* 41(7):4333–4346. https://doi.org/10.1016/j.ijhydene.2015.10.048.

Lewin, H. A., G. E. Robinson, W. J. Kress, W. J. Baker, J. Coddington, K. A. Crandall, R. Durbin, S. V. Edwards, F. Forest, M. T. P. Gilbert, and M. M. Goldstein. 2018. Earth BioGenome Project: Sequencing life for the future of life. *Proceedings of the National Academy of Sciences of the United States of America* 115(17):4325–4333.

Li, Q., Q. Zhao, Y. Hu, and H. Wang. 2006. Biotechnology and bioeconomy in China. *Biotechnology Journal: Healthcare Nutrition Technology* 1(11):1205–1214.

Lier, M., M. Aarne, L. Kärkkäinen, K. T. Korhonen, A. Yli-Viikari, and T. Packalen. 2018. *Synthesis on bioeconomy monitoring systems in the EU member states: Indicators for monitoring the progress of bioeconomy*. https://jukuri.luke.fi/handle/10024/542249 (accessed August 30, 2019).

Loizou, E., P. Jurga, S. Rozakis, and A. Faber. 2019. Assessing the potentials of bioeconomy sectors in Poland employing input-output modeling. *Sustainability* 11(3):594. doi: 10.3390/su11030594.

Maciejczak, M., and K. Hofreiter. 2013. How to define bioeconomy. *Roczniki Naukowe SERIA* 15(4):243–248.

Maisashvili, A., H. Bryant, J. M. Raulston, G. Knapek, J. Outlaw, and J. Richardson. 2016. Seed prices, proposed mergers and acquisitions among biotech firms. *Choices* 31(4):1–11.

Mateo, N., W. Nader, and G. Tamayo. 2001. Bioprospecting. *Encyclopedia of Biodiversity* 1:471–488.

Matyushenko, I., I. Sviatukha, and L. Grigorova-Berenda. 2016. Modern approaches to classification of biotechnology as a part of NBIC-technologies for bioeconomy. *Journal of Economics, Management and Trade* 14(4):1–14.

McCormick, K., and N. Kautto. 2013. The bioeconomy in Europe: An overview. *Sustainability* 5(6):2589–2608.

Meyer, R. 2017. Bioeconomy strategies: Contexts, visions, guiding implementation principles and resulting debates. *Sustainability* 9(6):1031. doi: 10.3390/su9061031.

MINAGRO (Ministry of Agroindustry). 2016. *Argentine bioeconomy: A vision from agroindustry*. Buenos Aires, Argentina: President of the National Ministry of Agrobusiness (English translation).

Naman, C. B., C. A. Leber, and W. H. Gerwick. n.d. *Modern natural products drug discovery and its relevance to biodiversity conservation.* http://labs.biology.ucsd.edu/schroeder/bggn227/Natural_Products_Biodiversity_Conservation_Chapter_Preprint-2.pdf (accessed August 30, 2019).

NASEM (National Academies of Sciences, Engineering, and Medicine). 2017. *Preparing for future products of biotechnology.* Washington, DC: The National Academies Press. https://doi.org/10.17226/24605.

NASEM. 2019. *Forest health and biotechnology: Possibilities and considerations*. Washington, DC: The National Academies Press. https://doi.org/10.17226/25221.

Natural Resources Institute Finland. 2019. *The principles for monitoring the bioeconomy*. https://www.luke.fi/wp-content/uploads/2018/11/22102018-principles-for-monitoring-eng-1.pdf (accessed July 26, 2019).

Nerlich, B. 2015. The bioeconomy in the news (or not). *University of Nottingham*, April 30. http://blogs.nottingham.ac.uk/makingsciencepublic/2015/04/30/the-bioeconomy-in-the-news-or-not (accessed October 6, 2019).

Nobre, G. C., and E. Tavares. 2017. Scientific literature analysis on big data and Internet of things applications on circular economy: A bibliometric study. *Scientometrics* 111(1):463–492.

OECD (Organisation for Economic Co-operation and Development). 2018. *Meeting policy challenges for a sustainable bioeconomy*. Paris, France: OECD Publishing. doi: 10.1787/9789264292345-en.

Parisi, C., and T. Ronzon. 2016. *A global view of bio-based industries: Benchmarking and monitoring their economic importance and future developments.* http://publications.jrc.ec.europa.eu/repository/bitstream/JRC103038/lb-na-28376-en-n.pdf (accessed August 30, 2019).

Pellerin, W., and D. W. Taylor. 2008. Measuring the biobased economy: A Canadian perspective. *Industrial Biotechnology* 4(4):363–366.

Perrings, C., S. Baumgärtner, W. A. Brock, K. Chopra, M. Conte, C. Costello, A. Duraiappah, A. P. Kinzig, U. Pascual, S. Polasky, T. Tschirhart,. S. Naeem, and D. Bunker. 2009. *Biodiversity, ecosystem functioning, and human wellbeing: An ecological and economic perspective.* Oxford, UK: Oxford University Press.

Petersen, A., and I. Krisjansen. 2015. Assembling "the bioeconomy": Exploiting the power of the promissory life sciences. *Journal of Sociology* 51(1):28–46.

Pfau, S., J. Hagens, B. Dankbaar, and A. Smits. 2014. Visions of sustainability in bioeconomy research. *Sustainability* 6(3):1222–1249.

Philippidis, G., A. I. Sanjuán López, E. Ferrari, and R. M'barek. 2014. *Employing social accounting matrix multipliers to profile the bioeconomy in the EU member states: Is there a structural pattern?* https://pdfs.semanticscholar.org/43e0/e0f4c97724d96b26991f3a2b0f2006b66204.pdf (accessed August 30, 2019).

Philippidis, G., R. M'barek, and E. Ferrari. 2016. *Drivers of the European bioeconomy in transition (BioEconomy2030): An exploratory, model-based assessment*. https://ec.europa.eu/jrc/en/publication/eur-scientific-and-technical-research-reports/drivers-european-bioeconomy-transition-bioeconomy2030-exploratory-model-based-assessment (accessed August 30, 2019).

Philp, J., and D. Winickoff. 2018. *Realising the circular bioeconomy*. Paris, France: OECD Publishing. http://www.wcbef.com/assets/Uploads/Publications/Realising-the-Circular-Bioeconomy.pdf (accessed August 30, 2019).

Reime, M., R. Røste, A. Almasi, and L. Coenen. 2016. *The circular bioeconomy in Scandinavia*. http://www.susvaluewaste.no/wp-content/uploads/2016/06/SusValueWaste-2016-The-circular-bioeconomy-in-Scandinavia.pdf (accessed July 25, 2019).

Ronzon, T., and R. M'Barek. 2018. Socioeconomic indicators to monitor the EU's bioeconomy in transition. *Sustainability* 10(6):1745.

Ronzon, T., S. Piotrowski, R. M'Barek, and M. Carus. 2017. A systematic approach to understanding and quantifying the EU's bioeconomy. *Bio-based and Applied Economics Journal* 6(1):1–17.

Saavoss, M. 2019. How might cellular agriculture impact the livestock, dairy, and poultry industries? *Choices*, Quarter 1. http://www.choicesmagazine.org/choices-magazine/submitted-articles/how-might-cellular-agriculture-impact-the-livestock-dairy-and-poultry-industries (accessed July 24, 2019).

Sasson, A., and C. Malpica. 2018. Bioeconomy in Latin America. *New Biotechnology* 40(Pt. A):40–45. doi: 10.1016/j.nbt.2017.07.007.

Schimmelpfennig, D. E., C. E. Pray, and M. F. Brennan. 2004. The impact of seed industry concentration on innovation: A study of U.S. biotech market leaders. *Agricultural Economics* 30(2):157–167.

Scordato, L., M. M. Bugge, and A. M. Fevolden. 2017. Directionality across diversity: Governing contending policy rationales in the transition towards the bioeconomy. *Sustainability* 9(2):206. doi: 10.3390/su9020206.

Sedjo, R. A. 2016. Preserving biodiversity as a resource. In *Global development and the environment*, edited by J. Darmstadter. Abingdon, UK: Routledge. Pp. 99–108.

Simpson, R. D., R. A. Sedjo, and J. W. Reid. 1996. Valuing biodiversity for use in pharmaceutical research. *Journal of Political Economy* 104(1):163–185.

Smeets, E. M. W., Y. Tsiropoulos, M. Patel, L. Hetemäki, S. Bringezu, M. A. H. Banse, F. Junker, P. Nowicki, M. G. A. van Leeuwen, and P. Verburg. 2013. *The relationship between bioeconomy sectors and the rest of the economy*. Working paper D1.1. Wageningen, Netherlands: Wageningen University & Research.

Soejarto, D. D., and N. R. Farnsworth. 1989. Tropical rain forests: Potential source of new drugs? *Perspectives in Biology and Medicine* 32(2):244–256. doi: 10.1353/pbm.1989.0003.

Sparks, T. C., D. R. Hahn, and N. V. Garizi. 2016. Natural products, their derivatives, mimics and synthetic equivalents: Role in agrochemical discovery. *Pest Management Science* 73(4):700–715. doi: 10.1002/ps.4458.

Staffas, L., M. Gustavsson, and K. McCormick. 2013. Strategies and policies for the bioeconomy and bio-based economy: An analysis of official national approaches. *Sustainability* 5(6):2751–2769.

Statistics Sweden. 2018. *The bioeconomy—developing new regional statistics*. Environmental accounts MIR 2018:4. https://www.scb.se/contentassets/89b174d9a3784532a1552c42330a446b/mi1301_2016a01_br_mi71br1804.pdf (accessed October 19, 2019).

Trigo, E. J., G. Henry, J. Sanders, U. Schurr, I. Ingelbrecht, C. Revel, C. Santana, and P. Rocha. 2013. *Towards bioeconomy development in Latin America and the Caribbean*. Bioeconomy Working Paper. https://agritrop.cirad.fr/567934/1/document_567934.pdf (accessed September 1, 2019).

U.S. OSTP (U.S. Office of Science and Technology Policy). 2012. *National Bioeconomy Blueprint (USNBB).* https://obamawhitehouse.archives.gov/sites/default/files/microsites/ostp/national_bioeconomy_blueprint_april_2012.pdf (accessed October 2, 2019).

U.S. OSTP. 2019. *Summary of the 2019 White House summit on America's bioeconomy.* https://www.whitehouse.gov/wp-content/uploads/2019/10/Summary-of-White-House-Summit-on-Americas-Bioeconomy-October-2019.pdf (accessed October 10, 2019).

Valli, M., H. M. Russo, and V. S. Bolzani. 2018. The potential contribution of the natural products from Brazilian biodiversity to bioeconomy. *Anais da Academia Brasileira de Ciências* 90(1, Suppl 1):763–778. doi: 10.1590/0001-3765201820170653.

von Braun, J. 2015. Science and technology policy to harmonize biologization of economies with food security. In *The fight against hunger and malnutrition: The role of food, agriculture, and targeted policies*, edited by D. E. Sahn. Oxford, UK: Oxford University Press.

von Hauff, M., F. T. Gottwald, K. Stöckl, J. Kurz, and C. Böker. 2016. Towards sustainable economies. In *Global stability through decentralization?* Cham, Switzerland: Springer. Pp. 117–138.

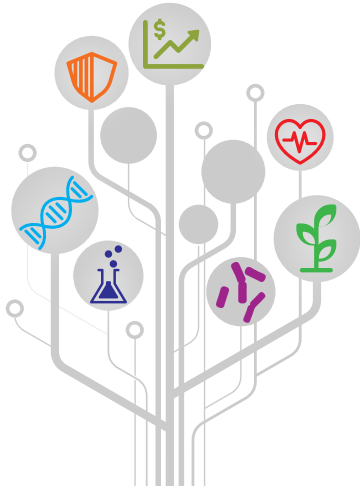
Wen, X., D. Quacoe, D. Quacoe, K. Appiah, and B. A. Danso. 2019. Analysis on bioeconomy's contribution to GDP: Evidence from Japan. *Sustainability* 11(3):712. doi: 10.3390/su11030712.

Wesseler, J., and J. von Braun. 2017. Measuring the bioeconomy: Economics and policies. *Annual Review of Resource Economics* 9:275–298.

Wierny, M., A. Coremberg, R. Costa, E. Trigo, and M. Regúnaga. 2015. *Measuring the bioeconomy: Quantifying the Argentine cas*e. Buenos Aires, Argentina: Grupo Bioeconomia.

Wreford, A., K. Bayne, P. Edwards, and A. Renwick. 2019. Enabling a transformation to a bioeconomy in New Zealand. *Environmental Innovation and Societal Transitions* 31:184–199. doi: 10.1016/j.eist.2018.11.005.

Zhang, S. 2017. *Genetically modified moths come to New York: A diamondback moth with altered DNA is being tested to control pests on cabbages*. https://www.theatlantic.com/science/archive/2017/09/genetically-modified-sterile-insects-take-flight/539040 (accessed August 30, 2019).



3 FRAMEWORKS FOR MEASURING THE VALUE OF THE U.S. BIOECONOMY

Summary of Key Findings

- The bioeconomy is a component of the larger U.S. economy, and its benefits are broad, ranging from life-saving health care solutions to the reduction of greenhouse gas emissions.
- The bioeconomy is cross-cutting. Many of the metrics commonly used to classify, collect, and report economic data fail to capture bioeconomic activity.
- A satellite account for the bioeconomy that includes intangible assets and its foreign supply chain has the potential to collect comprehensive data on the bioeconomy and to capture its potential for innovation and growth.
- Existing studies of the bioeconomy do not capture the activities encapsulated by the definition of the bioeconomy put forth in this report. In lieu of a satellite account, the committee devised its own measurement using available methods and data.
  - — Using 2016 data, the committee calculated that the bioeconomy accounted for about 5.1 percent of the U.S. gross domestic product (GDP). In dollar terms, this represents $959.2 billion.
  - — Should currently available biobased processes fully displace the traditional nonbiological processes, the U.S. bioeconomy could be as large as 7.4 percent of GDP.

Innovations in the bioeconomy often replace existing products. Because the benefits of such substitution may not be visible in traditional economic statistics, traditional measures of the bioeconomy may underestimate its size, its level of employment, and its impact on the economy overall. Further study (including benefits due to lower carbon consumption and improved health care solutions) would be needed to make such an assessment.

The breadth of the possibilities stemming from the translation of biological knowledge into meaningful applications is substantial. This chapter reviews the resources that the United States devotes to investments in this space and considers how one might measure the bioeconomy and assess its economic contributions to the larger U.S. economy. The chapter begins by characterizing the bioeconomy for economic analysis by examining the elements that set it apart from other sectors and reviewing the divergent approaches used to study the bioeconomy. It then addresses how to measure the bioeconomy by identifying approaches to valuing the bioeconomy and intangible assets, ultimately delineating a path forward.

Several factors make it difficult to measure the contribution of the bioeconomy to the overall economy: (1) definitions of the bioeconomy vary substantially; (2) the bioeconomy is tied to both basic science and its commercialization (innovation), suggesting that a broad range of activities is relevant to assessing the value of the bioeconomy; and (3) data on the bioeconomy have substantial gaps. Furthermore, it is difficult to define the economic boundaries of the bioeconomy, both because there are reasonably different ways to conceptualize the bioeconomy (see the discussion in Chapter 2) and because data identifying aspects of the bioeconomy are difficult to capture (e.g., identifying the fraction of a manufactured chemical that is produced through a biosynthetic pathway; see Chapter 2).

Concepts used to value the bioeconomy present additional challenges. Social welfare analysis, which attempts to quantify benefits to producers (e.g., economic rents[1]) and consumers (e.g., based on the difference between willingness to pay and price), is a particularly demanding approach to computing value and not ideal for valuing a sector as diffuse and challenging to measure as the bioeconomy. One could instead value the bioeconomy as the sum of the private values or value added of all

[1]The extra amount earned by a resource (e.g., land, capital, or labor) by virtue of its present use.

firms active in the sector, thus revealing the contribution of their production to overall gross domestic product (GDP).[2] In practice, however, even this approach is difficult to implement, as many of the firms that operate in this sector are diversified (e.g., Dow Chemical), and it is not possible to determine which fraction of total firm value is attributable to the bioeconomic aspects of such firms. In addition, many firms are privately owned (i.e., they are not public corporations), and their market value cannot be observed. Furthermore, focusing on private values where available (e.g., the sum of firm market values) excludes the considerable value of public-sector investments in university research and development (R&D) that supports the bioeconomy. For example, such an approach would exclude important public values associated with the bioeconomy, such as the potential benefits associated with a reduction in petroleum-based production.

Individual willingness to pay versus price issues aside, economic estimates of the value of the bioeconomy are limited in that they may not appreciate the full social value of its contributions. For example, if gasoline sales are replaced by an equal amount of biofuel sales, the two could show up in GDP calculations as equivalent, thus failing to capture the long-term environmental value to society.

CHARACTERIZING THE BIOECONOMY FOR ECONOMIC ANALYSIS

What Sets the Sector Apart?

One of the things that sets the bioeconomy apart is that it is not a discrete economic sector[3] like the production of automobiles or ketchup. As a result, no single approach or set of indictors provides a complete picture of the bioeconomy. Instead, the bioeconomy consists of a collection of products and services whose production is enabled by a set of related technologies (as delineated in the committee's definition and described in the landscape in Chapter 2) and that yields both inputs to and products

[2]GDP is a broad measure of a nation's overall economic activity. It may be viewed as the sum of gross value added (GVA) production across all sectors in the economy. Alternatively, it may be viewed as the value of all finished goods and services produced within a country's borders. In practice, there also are reconciling items in the accounting and issues regarding the prices that are used when summing value added across industries versus summing all final expenditures; for more detailed definitions, see https://www.bea.gov/help/glossary?title_1=All&title=GDP or https://stats.oecd.org/glossary/detail.asp?ID=1163.

[3]In this context, and in much of the report, the term "sector" is being used to describe a collection of activities that form part of the economy.

TABLE 3-1 Organizing Framework for Sectors and Technologies

		Sectoral Impact	
		Narrow	Broad
Applications within sector	Selective	Traditional sectors (e.g., ketchup production)	Selective yet broad impact (e.g., CRISPR; bioeconomy tools)
	Pervasive	Sector-specific (e.g., hybridization of corn)	General-purpose technologies (e.g., electricity, information technology, artificial intelligence)

SOURCE: Scott Stern, Massachusetts Institute of Technology, presentation to the committee, May 2, 2019.

of a range of economic sectors. To help provide an approach for characterizing the bioeconomy as a sector for economic analysis, Table 3-1 presents a typology of economic sectors and technologies. The typology distinguishes sectors on two dimensions, one (the columns of the table) that considers the breadth of a technology's impact across the various sectors of the economy, and a second (the rows of the table) that considers the scope of the technology's impact within each sector it affects. The columns distinguish between technologies that have a narrow impact on a small number of sectors, such as the technologies required to make ketchup, which impact mainly ketchup manufacturing, or hybrid corn, which affect mainly agriculture, and those that have a broad impact, such as electricity, information technologies, and applications rooted in the biosciences, which affect production processes across a wide range of sectors. The rows of Table 3-1 distinguish between applications that have a selective impact within each sector and those that have a pervasive impact in the sectors they affect. Whereas the bioeconomy has a selective impact within each sector it affects—for example, it affects parts of the production processes in most of the sectors in which it operates (e.g., the design of large-molecule drugs), general-purpose technologies, such as electricity and information technologies, have a pervasive impact on all aspects of the sectors they affect.[4]

According to this framework, the bioeconomy is a selective yet broad sector of the economy. It is "broad" because the technologies of the bioeconomy are likely to affect a wide range of industries, including those

[4]General-purpose technologies (GPTs; e.g., electricity, computers and communication technologies, artificial intelligence tools) are applicable in just about any sector of the economy. The concept of GPTs was introduced in the literature on the economics of growth by Breshnahan and Trajtenberg (1995).

associated with the production of food, fuel, and medicine, among others, but these technologies are not likely to displace all aspects of those industries. Additionally, as a result of innovation, the bioeconomy's outputs have benefits over and above the value of the resources devoted to producing them.

Many scientific breakthroughs associated with the bioeconomy (e.g., gene sequencing and gene editing) are sector-specific. They are "inventions in the method of invention" that create a situation in which biotechnology is a field subject to innovation in its processes (research) and a field whose conduct of research yields innovations for downstream use—that is, for consumers or other industries. The sector's upstream research inventions have been complemented by advances in computing and data analytic technologies that have led to, for example, dramatic declines in the cost of gene sequencing (see Figure 3-1, which shows that costs are declining faster than the rate at which Moore's Law predicted cost decreases in electronics) and shorter experimentation times in genomic research.

In budgets, however, personnel and other indirect costs typically loom many times larger than capital operating costs, suggesting that total upstream R&D costs may not be lower than they once were. The Biomedical Research and Development Price Index, which was developed by the Bureau of Economic Analysis (BEA) for the National Institutes of Health (NIH) to annually capture current personnel and materials costs, grows about 1 percent per year faster than economy-wide price measures, such as the Consumer Price Index or GDP price index.[5]

In part because the downstream payoffs to biotechnology are potentially large, the bioeconomy is characterized by large investments in basic and applied research that are funded by the federal government (much of this research is performed at universities or public research laboratories). Public outlays for "R&D in the life sciences" have historically been substantially larger than the outlays for other fields of science. An important function of the federal government not included in conventional R&D statistics is the cost of establishing and managing genomic and other data repositories (see below). The public availability of this information

[5]See https://officeofbudget.od.nih.gov/gbipriceindexes.html for the Biomedical Research and Development Price Index, which begins in 1950 and is available through the most recent year. Note that this index is built from detailed components and captures quality change in its components in two ways (Holloway and Reeb, 1989). First, the materials costs are built from Consumer Price Indexes and producer price indexes that are designed to be quality-adjusted. Second, to the extent that wages by detailed personnel component (e.g., faculty rank and federal General Schedule and step classifications) reflect differences in employee quality (i.e., marginal productivity), they also contribute to the index's control for quality change.

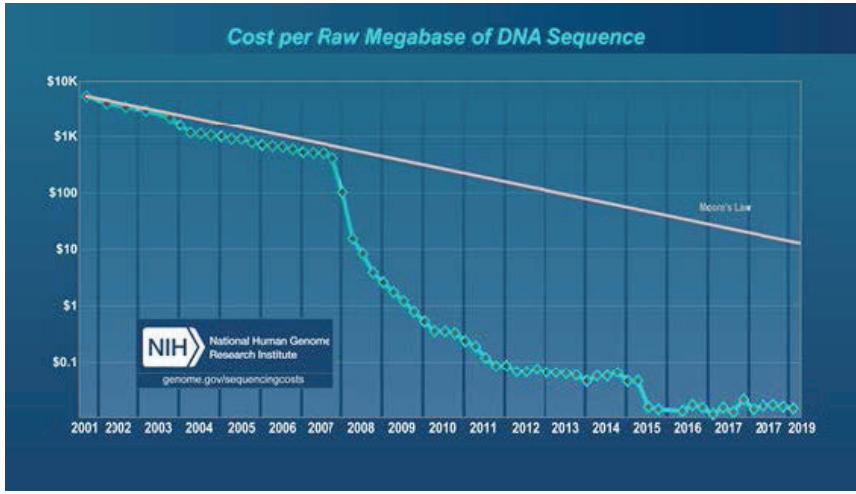


FIGURE 3-1 Sequencing costs. SOURCE: National Human Genome Research Institute. https://www.genome.gov/about-genomics/fact-sheets/DNA-Sequencing-Costs-Data (accessed August 1, 2019).

has aided the creation of new biobased products and processes for commercial gain while furthering scientific research.

Business R&D investments in the bioeconomy, particularly for the clinical trials stage of new drug development, loom large relative to R&D conducted by other industry sectors. Venture capitalists have recently geared up their investments in start-ups with an edge in synthetic biology. Although these investments are still small (and small in relation to all venture investments), this appears to be a fast-growing segment of the bioeconomy.

Two interrelated characteristics of the bioeconomy flow from the considerable size of its science base and the economic nature of its commercial applications. The first is that the applicability of a sector's science base (measured in terms of cited research articles in patents) is "close" to its commercial innovations. That is, the sector falls in "Pasteur's quadrant," meaning that it can be categorized as "use-inspired basic research," referring to the classification system for research developed by Donald Stokes (1997) (see Figure 3-2). In his work, Stokes divides research into three classes on the basis of whether the research has use considerations (purely applied research, such as that conducted by Thomas Edison) or is simply a quest for fundamental understanding (purely basic research, such as that conducted by Niels Bohr), or both (use-inspired basic research, such

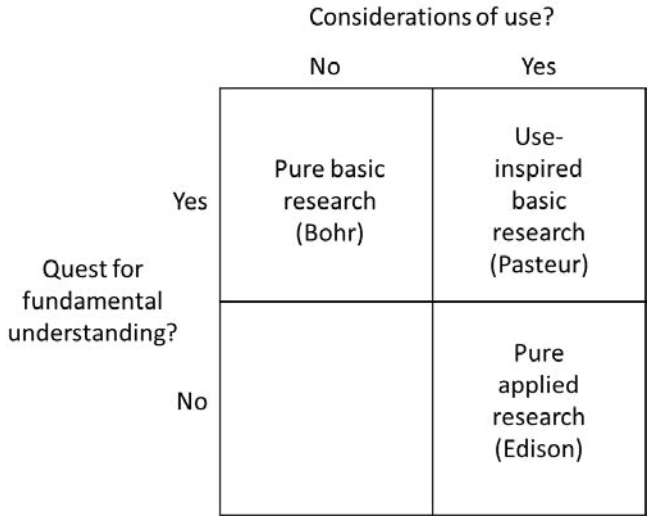


FIGURE 3-2 Quadrant model of scientific research. SOURCE: Adapted from Stokes, 1997.

as that conducted by Louis Pasteur) (Stokes, 1997).[6] This should not be surprising given the sector's use of breakthrough research that provides new tools that further advance commercial gain.

Second, the outcomes of many investments in bioeconomy innovation are highly regulated, as their potential for manipulating human, animal, and plant genetic material is closely connected with human health and the condition of environmental ecosystems. As a result, the bioeconomy's commercial innovation process is increasingly costly in relative terms. Firms throughout the larger economy are undergoing digital transformation in their business platforms and marketing processes, and those in sectors with containerized digital platforms[7] can not only implement

[6]The extent to which scientific advances support marketplace inventions is difficult to quantify, but this statement is generally consistent with theories that emphasize fruitful connections between certain types of patenting and prior scientific inquiry. Ahmadpoor and Jones (2017) devised a metric for the intellectual distance between patentable inventions and prior research to study the relationship between patents and scientific advances. The estimated distance varied by discipline, with multicellular living organisms and computer science having the shortest distance, and nanotechnology and biochemistry/molecular biology close behind (biotechnology was not identified separately).

[7]A containerized digital platform is a flexible, portable platform that allows for separating out the application's architecture into isolated environments that can be combined and organized without affecting the other elements of the application. For more information, see https://learn.g2.com/trends/containerization.

an innovation in back-end processes in nanoseconds but also conduct A/B tests on customers at little cost, regulations permitting.[8] Thus, there may be a growing relative cost premium for economic competencies for many types of firms in the bioeconomy compared with nonbioeconomy firms. Economic competencies are a broad category of intangible assets that include firms' go-to-market capabilities; see Annex 3-2 for further information on these assets.

These sector-specific aspects of the bioeconomy—its diffusion across industries, its potential for large societal benefits, its large science base and reliance on data-intensive research, the closeness of commercial innovation to a science base, and costs of commercial innovation that are fractions of large organizations' R&D budgets—make it difficult to track the bioeconomy's contribution to the economy and, as a result, assess its prospects for future innovation.

Official economic statistics are classified primarily by industry. This classification, as described above, is especially unhelpful for delineating much of the bioeconomy because its impact is selective within industry, and it operates across a wide array of industries. Furthermore, as noted earlier, official statistics cannot be used to translate the impact of the bioeconomy's innovations on social welfare as a result of the shortcomings of the economic estimates reflected in official statistics.[9] Finally, as spelled out in more detail below, the standard indicators used by science and innovation policy analysts do not include R&D in bioengineering and biomedical engineering in statistics on government R&D spending on life sciences or on business R&D in biotechnology; it is also likely that business investments in the building of private microbial databases are not included in biotechnology R&D.

Studies of the Bioeconomy: One Economy, Divergent Approaches

This report defines the U.S. bioeconomy as economic activity that is driven by research and innovation in the life sciences and biotechnology,

[8]A/B testing is a way to compare two versions of a single variable, typically by testing a subject's response to variant A against variant B, and determining which of the two variants is more effective. See Wikipedia, "A/B testing," for more information (https://en.wikipedia.org/wiki/A/B_testing).

[9]Although the price index was constructed by a researcher at BEA, the government agency that issues the national accounts for the United States, the work currently is not included in headline real GDP. Thus, one cannot look to official statistics on real output to "see" the welfare impacts of innovations in pharmaceuticals, although in time, BEA's initiative to build a health care "satellite" account may prove useful in this regard. Satellite accounts are discussed later in this chapter.

and that is enabled by technological advances in engineering and in computing and information sciences (see Chapter 1). Although existing studies do not generally align with this definition, current approaches to valuing the bioeconomy tend to fall into two broad categories. Some focus on industrial activity, aiming to detect how biobased activity may be substituting for petroleum-based activity (or promoting sustainability more broadly). Identified activities typically include products for downstream industrial use (including crops). Accounting for the value created in downstream use and industry input linkages is typically an important component of these studies. The second category consists of approaches that focus on biomedical activity and entail studying how breakthroughs in the biological sciences and biotechnology feed through to innovations in the pharmaceutical, medical device, and health care industries (as a whole or in part). Studies with this focus tend to look broadly at the innovation ecosystem, inclusive of the significant research in the biological sciences conducted in government and university laboratories.

Why such different approaches? The innovation ecosystem would appear to be as important for analyzing the drivers of bioindustrial activity as it is for analyzing biomedical activity. Enabling science and technology may be featured less in the former because measured R&D spending in the relevant industries does not loom as large as it does in the biomedical industries. The go-to-market costs of biopharmaceuticals include very costly clinical trials, and these trials are counted in R&D because they involve scientific experimentation and discovery. For biotechnology companies working to develop new microbial products for industrial use, the costs of testing and obtaining approval for new commercial applications are not commonly included in R&D because while these steps do require testing and experimentation, they are not counted as part of the basic research that led to the product's creation. It is also possible that emerging companies in the biotechnology space (including synthetic biology companies) escape the statistical net cast by R&D surveys because they are small and/or improperly sampled.[10] Still another possibility is that some companies' new-product discovery processes involve mainly modifying existing (or open-source) software tools to access microbial data. The creation and use of tools based on known methods, including the added

[10]The R&D survey conducted by the U.S. Census Bureau on behalf of the U.S. National Science Foundation has traditionally collected data on firms with five or more employees. Beginning with the survey for 2017 (unlikely to be published until 2020), R&D data will be collected from businesses with one or more employees.

value due to data processing that results from using existing tools, falls outside the scope of R&D surveys.[11]

All of these possibilities suggest that a targeted and specialized framework for analyzing the bioeconomy's innovation ecosystem is required—an approach that both looks broadly at investments in innovation (including investments in existing data analytic tools) and accounts for all bioeconomy-specific new product investments (e.g., improvements in the efficiency of regulatory testing). To encompass the full bioeconomy, this framework would capture data-driven innovations in health care that are intended to improve treatments (including drugs) on the basis of outcomes achieved relative to costs invested in designing the treatment. Finally, the framework would recognize that existing organizational structures do readily accommodate change, inclusive of data-driven approaches to revamping existing processes (from selection of patients for clinical trials to patient care itself). This implies recognizing that investments in new models are needed for organizations to execute data-driven plans, and that a period of time may elapse before the fruits of these changes will be seen in outcome data.[12]

MEASURING THE BIOECONOMY: APPROACHES FOR VALUATION AND IDENTIFICATION OF BIOECONOMY INTANGIBLE ASSETS

This section first summarizes existing approaches to studying innovation, focusing on those that attempt to place investments in knowledge, both scientific and commercial, at the center of the process. Second, in light of this discussion, the economic activities encompassed by the committee's definition of the bioeconomy, which include knowledge production as well as the tangible final and intermediate products produced by the bioeconomy, are described. Third, existing approaches and studies addressing measurement of the industrial bioeconomy are reviewed. Fourth, a range of estimates for valuing the bioeconomy, which potentially

[11]With regard to software and Internet applications, the R&D survey instructs respondents to include "only [those] activities with an element of uncertainty and that are intended to close knowledge gaps and meet scientific and technological needs" and to exclude "creation of new software based on known methods and applications." There are no instructions regarding the processing of data.

[12]This is in fact an argument made now for the case of artificial intelligence and its impact on general business productivity, but note that this topic is both frequently discussed in management consultancy newsletters and reports in the context of heath care organizations (e.g., Close et al., 2015) and widely acknowledged as a characteristic of innovation episodes (e.g., see the discussion in Brynjolfsson et al., 2018).

includes aspects of both the biomedical economy and intangible assets for the entire bioeconomy, are articulated.

Existing Approaches to Valuing the Bioeconomy

At the broadest level, the bioeconomy includes the economic activity stemming from advances in the life sciences. But while the broad scope of the bioeconomy is widely acknowledged, the bulk of academic and policy analysis has focused on biomedical activity and the impact of its innovations on human health (Hermans et al., 2007). By contrast, studies of bioindustrial activity attempt to capture the size and reach of biobased production activity (excluding biomedical activity). Whereas the previous subsections have reviewed general approaches to studying innovation, including measuring inputs to innovation, this subsection reviews approaches to measuring and valuing the agricultural and industrial bioeconomy (hereafter, referred to as industrial for the sake of brevity). Innovation outcomes in biopharma are discussed later in the chapter.

Broadly speaking, there are three approaches to measuring biobased production. Each begins by delineating the bioeconomy as a subsector of the total economy, and the most straightforward approach is to use the gross value added (GVA) of the delineated subsectors relative to total GDP (as raised earlier). A well-known study (Carlson, 2016) points out the limitations of this approach, suggesting that a delineation based on detailed products is more appropriate for the bioeconomy.

A second approach uses input-output (I-O) analysis to assess how the industry sectors included in the bioeconomy interact with other industry sectors in the broader economy.[13] This analysis can be conducted at the detailed product level, where the production of a particular "commodity" is connected to other economic activities, including impacts on final demand and/or industry value added. A step in this analysis can be the estimation of GVA for a delineated set of products. Although this approach narrows the estimate for these products (GVA for manufactured products is less than half of the gross value of the products), much of the industrial bioeconomy consists of physical products or industrial materials that are distributed to customers via intermediaries (retailers, wholesalers, transporters) whose margins are included in the final price and ultimate value of economic activity generated by biobased production. This suggests that the bottom line of the GVA approach—measurement of GVA in bio-producing sectors—is a partial impact that does not account

[13]I-O analysis is a form of macroeconomic analysis based on the interdependencies between economic sectors or industries.

fully for the interdependencies between industries, both backward and forward.

I-O analysis yields two levels of "multipliers" beyond the direct value of primary producer activity. These multipliers may be expressed relative to total final demand or relative to GVA of an industry. That is, the analysis calculates the effects of an extra unit of output in an industry on activity in other industries due to their interdependencies. As typically stated, the first multiplier, expressed relative to GVA of an industry, is calculated as the intermediate demand necessary to produce an additional dollar of value added for a particular type of product: it captures indirect effects via supplying industries to the industry producing the product ("backward linkages") plus those involved in the chain that supplies the product to ultimate users ("forward linkage"). This is called a type I multiplier. The second multiplier considers induced effects of the household and other final spending that results from the sum of direct and indirect effects (a type II multiplier).[14] Both multipliers rest on the assumption that inputs to an industry's production of output follow a fixed proportional relationship; this assumption is typically viewed as not very stringent for short-run analysis.[15]

Popkin and Kobe (2010) studied the major sectors of the U.S. economy, calculating type I multipliers for 15 major industry sectors, and found that the type I multipliers for the manufacturing, information, and agriculture sectors were the largest, while those for finance, retail trade, and wholesale trade were the smallest. Professional services, education, and government were below the median. Many key products of the bioeconomy are in high-multiplier industries (often called "upstream" industries, such as feedstocks), whereas others are in the low-multiplier ones (R&D services), suggesting that the diffuse nature of the industrial bioeconomy lends itself to an I-O approach.

A recent study commissioned by the U.S. Department of Agriculture (USDA) (Daystar et al., 2018) entailed an I-O analysis of industries covered by USDA's BioPreferred program. Although the components of that study included in this analysis do not align perfectly with the committee's tech-driven bioeconomy definition (see Chapter 1), the study's summary results reflect the potential size of the indirect and induced effects relative to the value added of important segments of the industrial bioeconomy.

[14]For further information regarding I-O modeling, see Miller and Blair (2009).

[15]Biobased production uses different inputs than petroleum-based production, however, and when these activities occur within the same industry, the I-O system's data will need to be augmented to reflect the appropriate inputs to each type of production. Failing to do so is not a first-order concern for calculating impacts in value terms (i.e., in dollars of value added), but for certain questions, such as how much carbon has been saved from the shift to biobased production, the validity of the underlying I-O relationships is relevant.

All told, those results suggest that the bioeconomy has a rather large type II multiplier (see Figure 3-3). The ratio of the total effect on value added to "direct" value added in USDA's BioPreferred industries was 2.92 in 2016. Referring to the stacked bar on the far right of Figure 3-3, the ratio of $459 to $157 is 2.92.

A third approach to valuing the U.S. bioeconomy is computable general equilibrium (CGE) analysis, which is grounded in formal economic theory.[16] This approach models the functioning of an economic system as a whole and focuses on the equilibrating role of the price mechanism in multiple markets (labor, capital, product). Models are usually calibrated to suit the analysis of an aspect of economic activity (e.g., energy consumption and climate change), and rely on consensus values for "deep," or fundamental, economic parameters (i.e., households' discount rate or the efficiency of firms' production processes). The models simulate economic outcomes under alternative assumptions and initial conditions. CGE models have proved fruitful in the analysis of climate change, where supplying a range of values for assumptions (e.g., for consumers' price sensitivity to energy prices or for the substitutability of energy for other factors of production) is not unrealistic (see the use of such a model in the

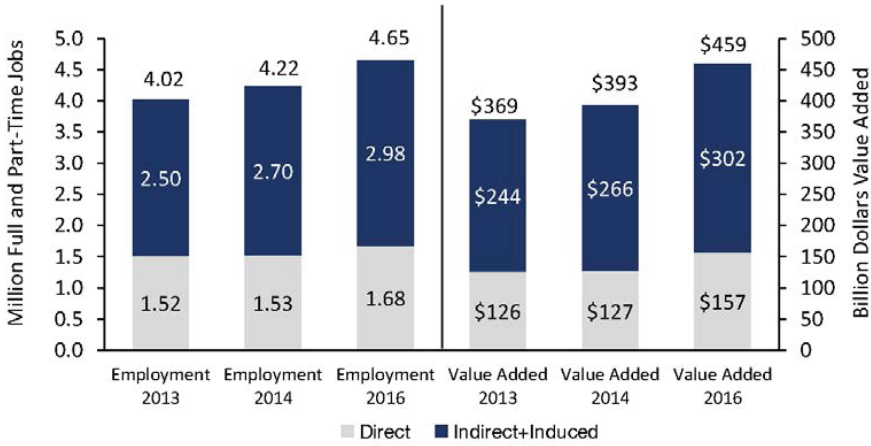


FIGURE 3-3 Economic impacts of the U.S. Department of Agriculture's BioPreferred Products list in 2013, 2014, and 2016. NOTE: The figure's legend for the type II multiplier ("Indirect+Induced") has been edited to align with terms used in this text. SOURCE: Daystar et al., 2018, p. ix.

[16]"CGE models are simulations that combine the abstract general equilibrium structure formalized by Arrow and Debreu (1954) with realistic economic data to solve numerically for the levels of supply, demand and price that support equilibrium across a specified set of markets." See www.rri.wvu.edu/CGECourse/Sue%20Wing.pdf and Arrow and Debreu (1954).

Fourth National Climate Assessment [USGCRP, 2018]). Some studies have analyzed the benefits to the environment of shifting to biobased industrial activity using stylized general equilibrium models (often in conjunction with results from an I-O analysis, as in Daystar et al., 2018), but these studies have tended to focus on traditionally defined sectors (e.g., all of agriculture, forestry, and wood products).

Selected studies that use these approaches are reviewed in Annex 3-1 as illustrative examples.

Identifying Intangible Assets

Existing approaches to measuring the bioeconomy need to account fully for investments in research, methods of invention, and data-driven commercial innovation. This involves recognizing that successfully developing and commercializing an innovation requires many ingredients other than scientific proof of concept. As described in Box 3-1, innovation requires market insights, data, and plans; product designs and market testing; branding; licenses; and human resources—all of which converge in business models and business processes. Spending on all of these components is included under the broad umbrella of intangible investment. Intangible investment has emerged as a key value driver in today's knowledge economy and a key factor in competitive advantage for firms.[17] A widely used framework for studying intangible investment is summarized in Annex 3-2.

The framework set out in Annex 3-2 is suitable for valuing intangible assets that are common to most companies in the U.S. economy, such as intellectual property, brand equity, software programs, and business process know-how, but two aspects of the framework require further development for in-depth analysis of the bioeconomy. The first is the fact that the public sector also creates and holds intangible assets, and it does so on behalf of society more broadly. Research on public intangibles is more limited than that on company intangibles, but the framework set out in Annex 3-2 can be adapted to the public sector.[18] The second is that the adaptation of the framework in Annex 3-2 to both the bioeconomy and the public sector involves putting the spotlight on *information assets*, or data.

In the public context, it is necessary to account for publicly collected data that are curated and issued for public use. Such assets loom large in

[17]For an accessible, recent review of this development in the context of the whole economy, see Haskel and Westlake (2017); for earlier reviews, see Corrado and Hulten (2010), NRC (2009), and OECD (2013). For developments at the firm level, see Lev (2001) and Lev and Gu (2016).

[18]See Corrado et al. (2017) for a systematic review and adaptation for public-sector activities and expenditures.

BOX 3-1
Innovation and Intangible Investment

What is *innovation*, and how does it differ from scientific invention? The Organisation for Economic Co-operation and Development periodically convenes a panel of experts to consider the definition of innovation. Published as the *Oslo Manual*, the definition distinguishes between innovation as an outcome (an innovation) and the activities though which innovations come about (innovation activities).

The 2018 version of the manual (OECD/Eurostat, 2018, p. 20) defines an innovation as "a new or improved product or process (or combination thereof) that differs significantly from the unit's previous products or processes and that has been made available to potential users (product) or brought into use by the unit (process)." This general definition is given a more precise formulation for use with businesses, which represent the main focus of the manual, although innovations in the delivery and utility of government services are also relevant to economic activity.

Intangible investment is defined as encompassing spending on innovation activities, that is, spending that may be expected to yield a return in future periods (beyond spending on tangible investments).[a] If a firm devotes resources to training its employees in a new company business process, such as the use of graph databases for organizing data on biomarkers, it does so with the expectation that operations will be leaner and more profitable in the future.

All told, intangible investment is a proxy for innovation inputs, that is, spending on the primary activities through which innovations come about. Investment in innovation is often thought to consist primarily of the costs of conducting science- or engineering-based research and development (R&D), but, in fact, innovation requires much more than spending on R&D. Other types of intangible assets include software tools, attributed designs, and marketing and other forms of organizational capability. See Annex 3-2 for a generic list of intangible assets commonly used in studies.

For the business sector of the United States, R&D investment is estimated to be less than one-fifth of total intangible investment.[b] While that may characterize parts of the bioeconomy, it may be less apt for other parts (such as the biomedical component). This suggests that, to view innovation in the bioeconomy, the traditional approach of focusing on private and public R&D should be expanded to consider:

- non-R&D intangible investments (generic list, as in Annex 3-2); and
- explicit treatment of public and private data, especially genomic sequence data, as assets.

---

[a]This definition is based on Corrado et al., 2005.

[b]Calculated using estimates for the U.S. business sector for the 5 years ending 2017 as reported at www.intaninvest.net.

many countries, and some public-use data spur economic development (as well as further research or cultural enrichment). For example, the U.S. Census Bureau's 1991 release of the Topologically Integrated Geographic Encoding and Referencing dataset is commonly credited with bootstrapping the nation's industries that develop, make, and use products based on geospatial data. Similarly, the public release of data from the National Aeronautics and Space Administration's Landsat satellite mapping program had a documented positive impact on the productivity of gold exploration projects (Nagaraj, 2018).

Although there is no one-to-one correspondence between the users of public biological data and particular industries of the U.S. economy, it is generally agreed that public biological data, especially digital data containing genomic sequences (digital sequence information, or DSI), have spurred commercial biotechnology-based economic activity.

Consider the GenBank sequence database, an open-access, annotated collection of all publicly available nucleotide sequences and their protein translations. This database and certain software used to access it are produced and maintained by the National Center for Biotechnology Information (NCBI), a division of the National Library of Medicine (NLM).[19] Since GenBank's inception at NCBI in 1992, use of the database and the number of sequences (i.e., data) it contains have grown at a very rapid rate (see Figure 3-4). This suggests that public data inputs have significant value for biomedical and bioindustrial scientific analysis.[20] If biological data assets are important inputs to further scientific and commercial advances, the beneficial impacts of open biological data will both spill over to productivity in the business economy (via new industrial and consumer biotechnology products) and generate benefits to human health via improved treatments for certain diseases (as discussed in detail in Chapter 6).

NIH reports that by 2016, the Human Genome Project had contributed to the discovery of more than 1,800 disease genes.[21] Taking advantage of

[19]NCBI is part of the International Nucleotide Sequence Database Collaboration, a joint effort to collect and disseminate genomic databases. The collaboration involves computerized databases in Japan and Europe (the DNA Data Bank of Japan and the European Nucleotide Archive in the United Kingdom); data submissions are exchanged daily among the collaborators.

[20]NIH supports many open-data repositories, including ClinicalTrials.gov, the world's largest publicly accessible database for exploring clinical research studies conducted in the United States and abroad. This database provides researchers and health care professionals—as well as the general public and patients and their family members—with easy access to information on clinical studies on a wide range of diseases and conditions. For a full list of open data at NLM, see https://www.nlm.nih.gov/NIHbmic/nih_data_sharing_repositories.html.

[21]See https://report.nih.gov/NIHfactsheets/ViewFactSheet.aspx?csid=45.

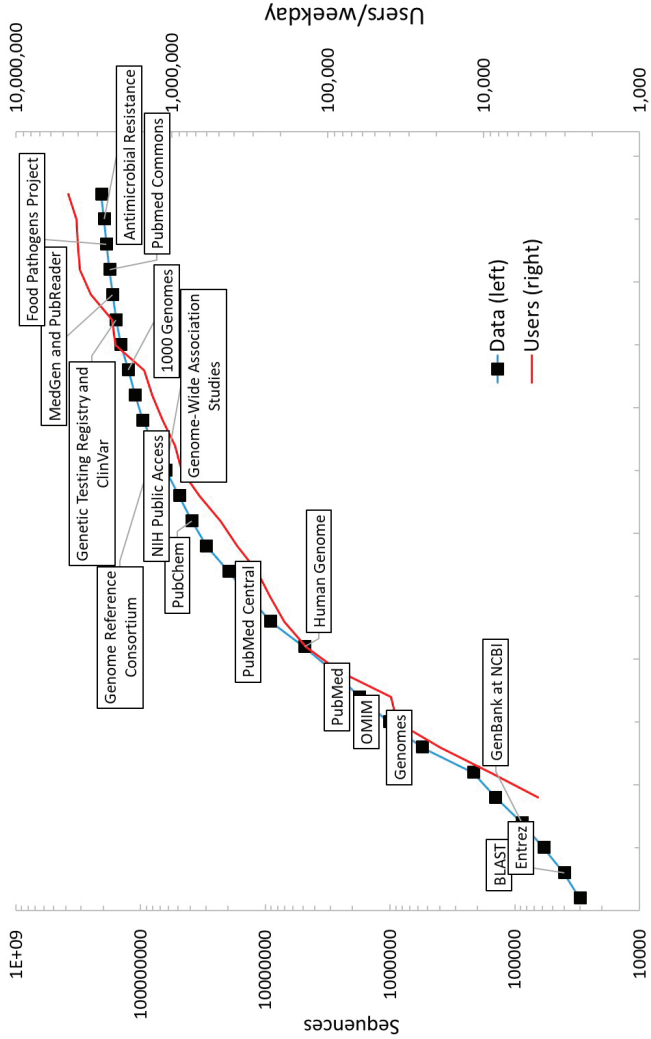


FIGURE 3-4 National Center for Biotechnology Information: Data (sequences) and users. SOURCE: Based on statistics reported at https://www.nlm.nih.gov/about/2019CJ.html#Budget_graphs (accessed May 4, 2019).

the publication of the human genome, today's researchers can find a gene suspected of causing an inherited disease in days rather than years. The costs of maintaining NCBI at current standards are rather small. NLM's annual budget hovered at about $400 million from 2015 to 2018 and rose to just under $442 million in 2019. This budget includes library operations and some intramural R&D, with NCBI accounting for about one-third of NLM's total budget in 2019, or $134 million.[22] If expansion of and/or improvements to the protection and curation of open data at NCBI are deemed warranted, it is worth noting that the current rate of public investment in making these assets freely available is very small relative to the likely benefits. While the economic value of NCBI has not been investigated specifically, economists have documented the importance of public databases for the progress of knowledge in science and innovation. These authors include Furman and Stern (2011), who demonstrate that public libraries for biological materials enhance the rate of knowledge generation associated with deposited materials; Biasi and Moser (2018), who show that reducing the cost of access to science books during World War II boosted scientific output in regions in which libraries purchased such books; and Furman and colleagues (2018), who document that patent deposit libraries had a positive impact on regional innovation in those areas that received such libraries in the pre-Internet age.

Valuation of Intangible Assets

Knowledge creation underlies the value of intangible assets. From an economic point of view, the value of a resource such as a gene database developed and owned by a for-profit company derives from its commercial value, that is, how the knowledge it contains can be used to introduce new and profitable products or services. For public companies, the firm's market capitalization will reflect this value to the extent that it is transparent (e.g., if the designs for new products are patented or if technology agreements between one company and another are public knowledge).[23]

[22]See https://www.nlm.nih.gov/about/2020CJ_NLM.pdf.

[23]Firm market capitalization captures market estimates of firm value, incorporating assessments of the values of tangible assets, such as plant and equipment; intangible assets, such as the expected fruits of R&D; and expectations about future macroeconomic, industry, and firm conditions. Recent research documents that the issuance of patents has a statistically significant and economically meaningful impact on firm value, as measured by market capitalization (Kogan et al., 2017). See also the Innovation-alpha Stock Price Indexes developed by M-CAM that outperform market indexes (e.g., S&P 500) using a quantitative, rule-based methodology that exploits the control and deployment of intellectual property, including patents, by public firms. See https://www.conference-board.org/data/bcicountry.cfm?cid=18 for further information.

The value for individual assets cannot readily be discerned this way, however; rather, the value of a company's portfolio of intangible assets is reflected in market capitalizations. This value encompasses not only the quantity and quality of the company's databases, patents, and other innovative property, but also its capabilities to exploit those assets for profit.[24]

Investments in certain intangible assets are included in GDP, and values for their corresponding stocks are estimated and published regularly as part of the U.S. national accounts. In other words, official economic statistics are available for the following types of intangibles:

- software and databases;
- R&D;
- mineral rights; and
- entertainment, artistic, and literary originals.

The official asset estimates are not based on market valuations but on a valuation method known as "replacement cost." The replacement cost method has long been used to value tangible assets, and these same methods are applied to intangible assets. Once intangible assets have been identified—a major step in its own right—replacement cost estimates for their values are developed from time-series data on investments using the perpetual inventory method (PIM). The following economic data and estimates are needed to implement the PIM:

- Time series for investments in each intangible asset
  - — Investments may be the value of purchases, or they may be the costs of developing the asset "in-house" (or both).
  - — Investments in both current dollars and constant (or "real") dollar terms are required.
- A depreciation rate for each intangible asset
  - — The idea is to capture the expected period of time for which the investment will yield a stream of returns (i.e., it is an *economic* rate of depreciation, not a rate of physical decay).
  - — Depreciation rates for some asset types may differ by industry, requiring multiple estimates for such asset types.

[24]This is not to say that business valuation analysts do not independently value intangible assets; they do, but typically in the context of an exchange between owners—that is, a transaction—as in a merger/acquisition (also for estate and gift tax purposes or as part of litigation). This leads to a situation in which company financial reports show values for intangible assets exchanged as part of a merger or acquisition, whereas values for assets created within firms that have not undergone a merger or acquisition are generally omitted; exceptions include certain mineral rights and, at the discretion of firms, software produced internally for the company's own use.

The PIM then cumulates real investments, period by period, after subtracting an estimate of economic depreciation during the period (the loss in the asset's value due to aging). This calculation produces an estimate of the volume of the asset stock; the value of the stock at replacement cost is obtained by multiplying the volume estimate by today's price.[25]

The advantage of the replacement cost approach that is used in national accounting is that it is comprehensive. Market valuations of public for-profit companies do not reflect the assets of privately held firms, which include start-ups, nor do they include the assets of private nonprofit organizations (e.g., private universities) or the nation's federally funded laboratory system. These are serious omissions for the upstream research-dependent bioeconomy, but all such institutions are in scope for national accounts. The valuation methods used for assets in national accounts do not depend on whether assets are held by the for-profit, nonprofit, or public sectors, although differences in the sectors' character, such as the longevity of services derived from the assets, are recognized: basic research in the life sciences funded and conducted by the public sector is deemed to yield assets with a longer service life than a commercial software package/tool.

The analysis of biological databases, especially DSI, requires a fresh look, beginning with defining the data types of interest and identifying where each type is being held, stored, and likely to be transformed for commercial use. In recent academic research using data pulled from LinkedIn, firm-level information on employees classified by skills held (e.g., data science) has been used to estimate the value of investments in artificial intelligence (AI) (Rock, 2018).[26] The idea is that AI may be included in the currently available estimates for software (albeit perhaps not comprehensively), but to analyze how investment in this area may be mismeasured and/or growing relative to other types of software requires a more granular approach. Rock's skills-based approach is potentially relevant for developing estimates of own-produced biological data knowledge as an intangible asset of the bioeconomy. If biological data knowledge is in fact the outcome of work done by employees with specialized technical skills (rather than by employees classified in a generic occupation, such as "software engineer"), this approach is promising.

[25]Note that a simple accumulation and correction for economic depreciation assumes that there no natural disasters or noneconomic events that diminish the volume of net stocks; in practice, these "other changes in volume" are accounted for when such events (e.g., a hurricane) destruct capital. Note also that replacement cost differs from both the historical cost approach used in U.S. Generally Accepted Accounting Principles–consistent company financial accounts and the mark-to-market, or fair value, method that the International Financial Reporting Standards allows.

[26]See also Brynjolfsson et al. (2018).

For the bioeconomy, skills may include proficiency in software such as the Basic Local Alignment Search Tool, ClustalW, DNA sequence analysis software, Mendel, PhyLOP, RTI International SUDAAN, SAS/Genetics, and Ward Systems Group GeneHunter.[27] As with the skills-based estimates of investments in AI versus investments in software, employees with these skills may be engaged in life sciences R&D, the idea being that even if life sciences R&D includes investments in biological data knowledge (in part or in whole), its own underlying dynamics are obscured.

With regard to valuing public databases, the value of the sequence data shown in Figure 3-4 can be considered as included in the value of R&D stocks in the bioeconomy's research fields. This is because the outcomes of the conduct of this R&D include not only new scientific findings (or new drugs), but also genomic data or other DSI made available to the public for future use via NCBI (as discussed earlier in the section on valuation of intangible assets). It is tempting to suggest that the relationship of biological databases to total R&D stocks is proportional (acknowledging that it may not be possible to specify an absolute value), but Figure 3-4 suggests that the number of NCBI users (an indicator of the user value of those stocks) is growing faster than the accumulation of those stocks themselves (which partly reflects outcomes of R&D). Perhaps, then, the pattern of use of the NCBI data could be exploited to estimate a depreciation rate for biological data stores, thereby providing an essential ingredient for their independent valuation. The same might be said of ClinicalTrials.gov if statistics on usership and age of data accessed were available.

When thinking about the value of data, Varian (2018) argues that data exhibit decreasing returns to scale, citing the example that an increase in the size of training data for AI algorithms yields diminishing returns in prediction accuracy. While this is an aspect of how the value of data declines (or depreciates) over time, consider the following: There are multiple dimensions of use for biological data—especially genomic data, or DSI—and the fruits of combining publicly available DSI with privately collected personal lifestyle data have yet to be fully realized (even if it could be said that the fruits of exploiting public DSI alone are diminishing). This observation suggests that diminishing gains to data may occur only as new dimensions/combinations in use diminish.[28] The capability

[27]These skills are listed on O*NET as skill requirements for a geneticist; see https://www.onetonline.org/link/tt/19-1029.03/43232605. Data on geneticists are obscured because the occupation is included in the higher-level category "Life Scientists, Other," which includes a collection of miscellaneous occupations, such as "Life Science Taxonomist." (O*NET is sponsored by the U.S. Department of Labor's Employment and Training Administration and is the nation's leading source of information on occupations.)

[28]Li and colleagues (2019) explore this observation for the influence of data assets on market valuations of digital platform companies.

to value long-lasting public DSI data is thus important for both businesses that use and augment these data and governments that support and fund the data's ongoing development.

Implications of Unmeasured Intangibles for Valuing the Bioeconomy

Studies that measure biologically based economic activity use several economic approaches. Each begins by delineating the bioeconomy as a subsector of the total economy. Typically, the bioeconomy is defined in terms of industry subsectors, and its economic contribution can then be measured from the national accounts using a value for the subsector's GVA relative to total GDP.

An industry's value added includes that industry's own production of investment goods, that is, its own conduct of R&D and generation of other intangible assets, including tools that enable data-driven capabilities. Some of these assets are not currently capitalized in the national accounts, suggesting that delineating the bioeconomy using official statistics for sector value added represents an approximation, indeed an understatement, unless this shortcoming is remedied.

A Path Toward Identifying and Valuing the Bioeconomy

There are no studies identifying and quantifying the bioeconomy using a definition consistent with that of this committee. In the following subsections, activities that fall within the committee's definition of the bioeconomy are described, and measurement tools required for future analyses of the bioeconomy are discussed.

Delineating the Bioeconomy

The primary user-driven segments of the bioeconomy—agricultural, bioindustrial, and biomedical—are considered first as the major categories of activity encompassed by the landscape and definition explored in Chapter 2. It is important to note that the committee's definition and explanation in the landscape discussion in Chapter 2 groups the activities within the bioeconomy into these three major scientific domains. However, when moving from a conceptual map based on scientific domains toward an economic mapping of the activities included in the bioeconomy, the groupings change to account for the limitations of the current classification system. For example, when considering the scientific domain of agriculture, the committee identified crops (genetically engineered or created via marker-assisted breeding programs) as being included in the

bioeconomy (criteria #1 and #2; see Chapter 2). The committee also identified as being included the use of plant biomass in a downstream bioprocessing and/or fermentation process utilizing recombinant DNA technology (criterion #4; see Chapter 2). However, in an economic mapping, the economic activity stimulated by plant biomass is grouped with the industrial activity of biobased chemical production. This is a function of how and where the economic activity is collected, categorized, and attributed.

A study whose circumscribed bioeconomy activities are wholly contained within the committee's definition (Carlson, 2016, 2019) is reviewed in detail in Annex 3-1. Like the committee, Carlson focuses on agricultural and industrial revenues generated through the use of genetically modified (GM) biological organisms and systems. His accounting includes crops, biopharma and biologics, and biobased industrial products (e.g., biofuels, enzymes, and biochemicals). He acknowledges that North American Industry Classification System (NAICS) code categories are too broad to capture value added in these activities accurately. Indeed, a major contribution by Carlson (2016) is his suggestion to revise the system used to classify official statistics on economic activity by industry (see Box 3-2). As noted in Annex 3-1, Carlson focuses mainly on business-to-business activity, which leaves out the value added in products that are further processed and/or are delivered to consumers (e.g., biobased plastic bottles [although resins are included]), in contrast to the committee's approach.

Moving from primary segment to the details that would enable data capture requires identifying the relevant codes within that category that cover the scope of the committee's definition. For example, biomedical activity usually encompasses three relatively well-defined (yet detailed) industry sectors: pharmaceuticals, biotechnology R&D services, and electromedical equipment and medical instruments (Hermans et al., 2007). In NAICS, the system currently used to classify economic activity by industry,[29] these industry sectors are represented by four categories of codes: Pharmaceutical and Medicine Manufacturing, NAICS 3254; Electromedical Instruments Manufacturing, NAICS 334510, 334516, and 334517; Surgical and Medical Instrument Manufacturing, NAICS 339112; and Research and Development Services in Biotechnology (except nanobiotechnology), NAICS 541714. According to the committee's definition, NAICS 541715 should also be partially included, as it covers Research

[29]NAICS organizes industry activity by sectors and subsectors using a hierarchical structure and six-digit code. The first two digits identify the sector, the third digit identifies the subsector, the fourth digit identifies the industry group, and the fifth identifies the NAICS industry. The first five digits are standardized across the United States, Canada, and Mexico. Each country can use a sixth digit to identify the specific national industry (which is therefore specific to the country and not standardized). For examples and more information, see https://www.census.gov/programs-surveys/economic-census/guidance/understanding-naics.html.

BOX 3-2
Updating the NAICS and Beyond

Carlson (2016) proposes three additions to the *industry* classification system used to collect data on the U.S. economy—the North American Industry Classification System (NAICS). In his own words, they are as follows:

> First, there should be a new code clearly identifying "production units" that manufacture protein and nucleic acid-based drugs as a subset of "pharmaceutical and medicine manufacturing" (3254). Second a code should be included under "chemical manufacturing" (325) that captures nonpharmaceutical, cell-based production of chemicals and materials. It is unclear how best to distinguish chemicals produced from cells that have been subjected to mutation and selection from those produced from cells whose genomes have been directly modified. An additional code may be necessary for this purpose, as well as one that anticipates the emergence of cell-free biological production systems. Third, as there is no clear code for biofuels and no code inclusive of biodiesel, new codes should be established for biofuels to distinguish them from petroleum-based fuels.

By "beyond," Carlson is referring to the classification system for *products* according to their use in the market—the North American Product Classification System (NAPCS). For information on NAPCS, see https://www.census.gov/eos/www/napcs/napcstable.html.

Carlson continues:

> Finally, although it would be useful to have high-quality, fine-grained data elucidating exactly which chemicals are produced, and with which organisms and processes, the NAICS may not be the ideal mechanism to gather all such information. Instead, the NAPCS, which is intended to classify products by use in the market, may be a more appropriate means to distinguish between biotechnological products intended for increasingly varied markets. For example, it could be argued that nonpotable ethyl alcohol produced by fermentation should not be segmented by NAICS codes into fuel and nonfuel uses, as long as the codes make it distinguishable from the same molecule produced by synthetic chemistry. Rather, the different uses of ethyl alcohol as a fungible molecule may best be accounted for at the point of use via the NAPCS. Similar market-level differentiation among biological products may be a better means to characterize the bioeconomy. The NAPCS appears to be underutilized for this purpose, save for a fine-graining of "scientific research and development services" into many flavors of biological science and engineering….

SOURCE: Excerpt from Carlson, 2016, p. 251.

and Development Services in the Physical, Engineering, and Life Sciences (except Nanotechnology and Biotechnology). According to the North American Product Classification System (NAPCS)[30] product list for NAICS 5417 (see Box 3-2), the latter would include bioengineering and biomedical R&D services, which covers the mechanical engineering of robotic systems for health care.[31] Many studies of biotechnology consider activity in NAICS 541714 as in scope for their analysis, but this approach misses the other life sciences, biomedical engineering, and bioengineering R&D services activity included elsewhere in the overall R&D services industry.

Moving from the three primary segments (agriculture, bioindustrial, and biomedical), the committee needed to determine the subset of the primary segments for which economic activity data are captured. Thus, the committee identified the six segments within the broad category of goods and services, which includes materials, business services, and consumer products. At the level of these segments, the following six segments are taken as an approximation of the bioeconomy, as best as can be determined from the available data, and recognizing that they incompletely capture the bioeconomy as the committee has defined it:

- GM crops/products;
- biobased industrial materials (e.g., biobased chemicals and plastics, biofuels, agricultural feedstocks);
- biopharmaceuticals and biologics, other pharmaceuticals;
- biotechnology consumer products other than drugs (e.g., genetic testing services);
- biotechnology R&D business services, including laboratory testing (kits) and purchased equipment services (e.g., sequencing services); and
- design of biological data-driven patient health care solutions (i.e., precision medicine inputs), exclusive of patient care services per se and drugs counted elsewhere.

The bioeconomy also includes investments in specialized equipment and services, including

[30]NAPCS is a coding system that categorizes products (good and services) independently of industry of origin. These codes can be linked back to the NAICS industry classification and are also consistent across Canada, Mexico, and the United States. For more information, see https://www.census.gov/programs-surveys/economic-census/guidance/understanding-napcs.html.

[31]See https://www.census.gov/eos/www/napcs/finalized/web_5417_final_reformatted_edited_US060409.pdf.

- specialized equipment purchased for use in bioeconomy-related research, product development, and testing (e.g., mass spectrometers, sequencing machines);
- specialized instruments developed for research laboratories and medical care (selected medical devices, including medical robots); and
- long-lived services (intangible assets) purchased by bioeconomy firms for product development (e.g., specialized software and consulting services, including data analytic services).

In addition, the bioeconomy includes the production of intangible assets within bioeconomy organizations for their own use, such as

- own production of value added via the development of databases for further use in product development and testing (as in the example given in the earlier section on estimation of investments within organizations); and
- R&D and other generic intangible assets, including training of employees in specialized bioeconomy skills.

The activities listed above reflect the orientation of this committee's definition of the bioeconomy toward activities stemming from advances in the life sciences as enabled by engineering, computing, and information sciences. The list of activities is highly diverse and ranges from GM crops to such activities as the production of medical robots and biological data as an intangible asset. The committee's definition potentially encompasses innovative applications of precision medicine to nonscientific domains (patient care or health insurance), although these extensions are not included in this economic analysis. All told, a comprehensive and "living" approach to measurement is necessary (i.e., one that encompasses future activities affected by biobased technological advances).

A Satellite Account for the Bioeconomy and Its Assets

An accounting of the bioeconomy as a subsector of the economy requires a comprehensive set of measurements. A dedicated bioeconomy satellite account built as an adjunct to the U.S. national accounts would provide a necessary tool for economic analysis of the bioeconomy.

A satellite account is a system of economic data that portrays expenditures, production, and income generated by a defined set of activities. Satellite accounts typically design tables with specific users in mind (up to the limits of the data), especially when the extent of the detail on production and expenditures illuminates a collection of activities not aggregated elsewhere in economic data (see Box 3-3).

BOX 3-3
Satellite Accounts

According to the U.S. Department of Commerce's Bureau of Economic Analysis (BEA), satellite accounts are

> supplemental accounts that expand the analytical capacity of the main system of accounts by focusing on a particular aspect of economic activity. Satellite accounts are linked to the main accounts but have greater flexibility in providing more detailed information or in using alternative definitions, concepts, and accounting conventions. For example, BEA's travel and tourism satellite account provides detailed information on output, supply, demand, and employment for those industries.

National and international economics statistical agencies have often adopted satellite accounts for economic activities that do not fit neatly under more traditional definitions in systems of national income accounts. Besides tourism, satellite accounts have been proposed to better measure agribusiness activities (Arboleda, 2001; NASEM, 2019). Other examples of satellite accounts include the digital economy, environment, and unpaid household work. Satellite accounts may be used to explore new data collection and reporting methods and to develop new accounting procedures that, once accepted, could become part of standard national income accounting procedures.

As with tourism, the bioeconomy spans several traditional economic sectors and includes activities not fully captured in traditional sector definitions. Because activities within the bioeconomy will continue to evolve, data collection and accounting procedures may also need to evolve to enable measurement of the bioeconomy.

A satellite account system for the bioeconomy would, ideally, develop the appropriate interindustry relationships for biobased production, include a full accounting of intangible assets and bioeconomy databases, incorporate quality-adjusted price deflators for relevant products (e.g., biopharmaceuticals and biomedical equipment), and facilitate accounting for certain environmental benefits (e.g., as in Daystar et al., 2018). The sources of supply, domestic and foreign, for bioeconomy products and for inputs to bioeconomy domestic production should also be illuminated, along with financial flows relating to inward and outward transfers of the bioeconomy's technology and information assets, necessitating the development of new data.

The design of the bioeconomy satellite account could possibly exploit available administrative data,[32] as well as U.S. Census Bureau

[32]"Administrative data" refers to data collected and maintained by government agencies and used to administer (or run) their programs or provide services to the public (e.g., Medicare data).

survey-based microdata, to ensure the necessary scope and coverage. Additionally, the horizon-scanning and forecasting efforts envisaged in Chapter 6 could provide further insight into designing the bioeconomy satellite account and ensure its utility for addressing specific policy and forecasting questions.

Valuing the Bioeconomy

In lieu of a satellite account, the committee approached valuing the bioeconomy and its intangible assets in the context of the committee's definition as a pilot experiment: What can existing tools, data, and studies demonstrate about the bioeconomy and its reach? Consider, then, marrying the committee's components discussed earlier with the I-O approach set out in Daystar et al. (2018). The Daystar et al. (2018) study provides value added for many relevant bioeconomy products, estimates that are not otherwise available using official data alone.

A Valuation Pilot Experiment and Framework

Can elements from Daystar et al. (2018) be supplemented with others to bridge at least most of the gap between the relevant products in that study and the more comprehensive set of goods and services covered by the committee's definition? The answer to this question would appear to be yes, by using elements from Carlson (2019) where possible, by estimating gross output values for bioeconomy goods and services and converting them to GVA using the ratio of the latter to the former for the industry as a whole, and by drawing on a set of estimates for R&D and other intangible investments by detailed industry conforming to the detail set out by BEA in the U.S. national accounts. Box 3-4 summarizes the steps taken to generate the figures developed for the pilot experiment.

The specific segments of the bioeconomy included in the experiment's estimates are listed in Table 3-2 and cover items that can readily be identified based on previous studies and simple extensions based on the committee's definition (e.g., the addition of electromedical equipment). The conclusion of this pilot experiment is not meant to be definitive, and may err either on the short side to the extent that the delineation of activities associated with the committee's tech-driven definition falls short or on the high side to the extent that too much of an identified activity is ascribed to the bioeconomy.

That said, and as may be seen from inspection of Table 3-2, publicly vetted estimates (or simple translations of gross output data) are available for most of the segments listed in the earlier subsection describing the path toward identifying the value of the bioeconomy. Where segments

BOX 3-4
Framework for Valuing the Bioeconomy

1. Set boundaries for the definition of the bioeconomy to identify primary segments of interest (see Chapter 2).
2. Identify subsets of the primary segments to be included, encompassing relevant bioeconomy-specific equipment investments (e.g., sequencing machines) and services (e.g., biotechnology patent and legal services) and intangible assets produced and/or curated for use by the sector (e.g., genomic databases).
3. Identify the relevant production data that map to the delineated bioeconomy segments.
   a. Table 3-2 provides a mapping based on the North American Industry Classification System (NAICS) codes currently used by the U.S. Census Bureau to collect detailed data on the value of production.
      — Certain bioeconomy activities are inherently narrower than existing NAICS codes, and measuring those activities requires developing estimates based on auxiliary sources (or new NAICS codes), or building new aggregates from establishment-level survey or administrative microdata.
      — For each biobased production activity, determine the portion that is currently versus potentially (under existing technology) biobased (e.g., determine what percentage of plastics are made through a biobased process).
   b. Obtain estimates for value added for each relevant bioeconomy activity based on the same methods and data used in national accounts ("GDP by industry").
   c. Determine appropriate interindustry linkages and sources of supply (i.e., domestic versus foreign) and estimate relevant input-output "multipliers" based on these linkages.
4. The sum of value added estimates is the direct impact of bioeconomy production on the U.S. economy; the additional value added implied by input-output multipliers estimates the total contribution of the bioeconomy to the U.S. economy.

involve biobased production, two value added estimates for the activities listed in columns 2 and 3 of the table are used: the first, shown in column 4, represents an estimate of the current value added in biobased production, and the second is an estimate of the potential for biobased production (using current technology). These estimates come from Daystar et al. (2018), where that study is listed as a source in column 3 of the table. For other estimates, modest assumptions were made based on the available literature (e.g., that biopharma now accounts for 25 percent of all pharmaceuticals, and that its potential is 80 percent, where the upper limit represents the capability possessed by the leading-edge global firm in 2014) (Otto et al.,

TABLE 3-2 Illustrative Bioeconomy Segments and Their Value Encompassed by the Committee's Definition

	Segments	Classification (North American Industry Classification System [NAICS] code, where relevant)	Source of Estimate for Value Added[1]	Value Added in 2016 (millions of dollars) Current	Potential
Private Industry Sector Segments					
1.	Crop products	11111-6, 11119, 111900pt	Committee calculations; Carlson (2019)	36,740	46,141
2.	Biorefining (food)	311210, 221, 224, 225; 311300	Daystar et al. (2018)	3,023	36,830
3.	Biofuels (ethanol)	324110pt	See note 2	8,361	12,553
4.	Biopharmaceuticals	325412pt	See note 3	31,118	99,575
5.	Biologics (enzymes)	325414	Daystar et al. (2018)	16,918	16,918
6.	Other pharmaceuticals	325412pt	See note 3	93,354	24,894
7.	Biobased petrochemicals	35211	Carlson (2019)	6,726	16,304
8.	Other enzymes	32519pt	Daystar et al. (2018)	11,918	11,918
9.	Other biobased chemicals	325211, 32519, 32522, 325510, 325998, 325611, 325612, 325520, 325991, 325992, 325910, 325613	Daystar et al. (2018)	8,081	50,505
10.	Biobased plastic products	326	Daystar et al. (2018)	997	68,436

11.	Electromedical instruments	334510, 6, 7	Gross output (GO) adjusted to gross value added (GVA)	49,636	49,636
12.	Surgical and medical instruments	339112	GO adjusted to GVA	28,153	28,153
13.	Bioeconomy R&D services	541714, 541715pt	Annex 3-1 discussion	43,090	43,090
Intangible Investments Not Included in Value Added as Detailed Above					
14.	Data services/software purchases	Private bioeconomy segments listed above	National accounts and INTAN-Invest	5,615	7,880
14a. Memo:		*Private health care organizations*	INTAN-Invest	15,194	—
Public and Nonprofit Sector Segments					
15.	R&D	Life sciences, bioengineering, and biomedical engineering	National accounts, NCSES surveys	44,546	44,546
16.	Software and data-related analytic services	Classification of functions of government, health	National accounts and SPINTAN project[4]	14,190	14,190
			Total[5]	343,730	571,569

NOTES:
1. Reports the source for the estimate of the share of national accounts value added in the "nearest" available detailed industry. The final value added estimate for each activity also includes the contribution of intangibles not in the national accounts developed from a detailed version of the estimates reported at www.intaninvest.net.
2. Estimate based on fraction of gasoline that is ethanol. Biomass electric power generation is not separately listed; available estimates suggest value added in this activity was $635 million in 2016.
3. Estimate based on Otto et al. (2014) and the National Center for Science and Engineering Statistics Business R&D and Innovation Survey data reviewed below in the section on the direction of the bioeconomy.
4. SPINTAN (Smart Public Intangibles) refers to a European Commission Framework–financed project whose research consortium included The Conference Board. See www.spintan.net. The estimates of public- and nonprofit-sector intangibles developed for the SPINTAN project are designed to complement those for the market sector found at www.intaninvest.net.
5. Excludes line 14a.

2014). Further study is needed to refine the estimates of potential biobased production in the delineated industries, especially pharmaceuticals (the Daystar et al. [2018] study does not include pharmaceuticals).

The actual and potential estimates of value added of existing industries serve a dual purpose. First, they are summed to value the bioeconomy. Second, the implied shares of value added of existing industries are assumed to approximate the bioeconomy's share of the industry's total investment in intangible assets (i.e., the potential column demonstrates the full value of all activities contained within the listed segments, demonstrating the potential for the bioeconomy to grow within a given segment). These shares are then used (1) to include own production of non-national accounts intangibles in value added; and (2) to calculate purchases of services related to software and biological data.

With regard to investments in intangible assets, the following was done. First, all value added estimates for segments shown in Table 3-2 were based on national accounts estimates of value added that include own production of software and R&D. Second, estimates of non-national accounts intangible assets for each bioeconomy segment listed in Table 3-2 were obtained using each segment's share of value added in the industry-level data used to develop industry-level estimates of intangible investment; the industry-level intangible asset estimates were based on estimates that followed methods documented at www.intaninvest.net. Third, the value of purchased software assets and data analytic services was accounted for separately using the same shares. Finally, the conduct of bioeconomy R&D by the government or universities was included in the value of bioeconomy activity as a separate, delineated activity.

Regarding biological data, an assumption was made that a firm's own production of databases is included in national accounts estimates of software; likewise for their purchases, to the extent a market transaction takes place. While this constitutes a lower bound, note that investments in data analytics by firms in the bioeconomy are reflected in their purchases of (1) computer design and related information technology consulting services and/or (2) management consulting services. These items are not included in the national accounts estimates of intangibles, but we have added available estimates of spending on these activities by bioeconomy firms. For the public sector, the value of the investments in software and computer design consulting (our best proxies for investments in data), as estimated for the function of government circumscribed as "health," also is included.

Contribution of the Bioeconomy to U.S. Value Added

The sum of the direct impact of value added in bioeconomy industries shown in column 4 of Table 3-2 totals $402.5 billion, or 2.2 percent of GDP in 2016 (see Table 3-3). If biobased production were at its potential level, the value added figures shown in column 5 of Table 3-2 would be $571.6 billion, or 3.1 percent of GDP (note that only the private economy is affected by shifts toward biobased production within an industry). The subtotal for private value added in the bioeconomy was nearly 1.8 percent of GDP in 2016, and its estimated potential level was 2.7 percent of GDP.

To estimate indirect and induced effects, a multiplier of 2.5 was applied to private bioeconomy economic activity; this multiplier is substantially lower than the implicit multiplier in Daystar et al. (2018) as a result of the inclusion of R&D services, pharmaceuticals, selected equipment, and other intangibles. These latter segments are large relative to other private biobased activity, and a multiplier closer to that for overall manufacturing (2.41 from Popkin and Kobe [2010] as quoted above) is more appropriate. Then a multiplier of 1.7 was applied to government and higher-education activity (from Popkin and Kobe [2010]). Without further study, it is impossible to be more precise, an observation that reinforces the need for a bioeconomy satellite account that details the appropriate interindustry linkages for relevant economic activities.

After applying the multipliers described above, economic activity driven by the bioeconomy is estimated to have accounted for nearly 5.1 percent of GDP in 2016, and would have accounted for 7.4 percent with biobased production at its estimated potential level. We stress that this guideline for the size of the bioeconomy is offered only as suggestive of the current state of the literature in the form of a rough estimate. It is rough because the committee's definition of the bioeconomy is meant to be "living," and there are significant gaps in the available data. Advances in technology will affect circumscribed activities and the evolution of the potential of bioeconomy production (e.g., this potential could be larger by 38 percent if a modest estimate of the delivery of biodata-based precision medicine solutions at the point of care were included in bioeconomy activities).[33]

[33]Health care services (excluding drugs, insurance, and administrative costs) directly accounted for 10 percent of U.S. GDP in 2016, 27 percent of which represented physician services. If this figure is used as a marker for the value of point-of-care services, it suggests that another 2.7 percent of U.S. GDP is potentially (directly) impacted by the bioeconomy.

TABLE 3-3 Summary of Illustrative Bioeconomy Valuation Experiment

	Major Sector	Value Added in 2016 (billions of dollars) Current	Potential
Direct contribution:			
1.	Private industry	343.7	512.8
2.	Public/nonprofits	58.7	58.7
3.	Total	402.5	571.6
4.	*Percent of GDP*	*2.2*	*3.1*
Including indirect and induced effects:			
5.	Private industry	859.3	1,282.1
6.	Public/nonprofits	99.9	99.9
7.	Total	959.2	1,381.9
Percent of GDP		*5.1*	*7.4*

SOURCES: Table 3-2 and Box 3-4 for bioeconomy valuation. Bureau Economic Analysis for U.S. GDP in 2016, which was $18,715 billion.

Valuation of the Bioeconomy's Intangible Assets

A takeaway from the earlier discussion of the valuation of intangible assets is that using a national accounts approach to estimate the value of an asset stock requires a time series of investments in the asset and a rate of depreciation for the asset. From the above, estimates of the private bioeconomy's intangible investments are available for 1 year (2016) (estimates of biobased production in an industry relative to the industry's total production over time are not readily available). The lack of readily available time-series information on biobased production shares is another example of the need for more complete data on the bioeconomy such as would be provided by a satellite account.[34]

Regarding biological data, even if analysis in line with the bioeconomy components listed in Table 3-2 were possible, the results would not necessarily be comprehensive. Analysis of biological data requires identifying the sectors and activities that hold large quantities of such data. The public sector is, of course, a large holder, as previously described, but the private health care sector also invests heavily in biological data

[34]One could consider the bioeconomy's intangible investments via funding for R&D performed by the public and nonprofit sectors (the last two components listed in Table 3-2), which do not rely on production shares. All told, estimates of these values alone would not be informative as to the bioeconomy's stock of intangible assets.

(although not necessarily genomic data), and these investments would not be included if valuation of biological data were confined to the bioeconomy as delineated in Table 3-2. For data services and software alone, spending by the private health care sector is nearly three times what is currently spent by private industries included in the bioeconomy (compare line 14a with line 14 in Table 3-2). The analysis of biological data stores requires a fresh look, beginning with defining the data types of interest and identifying where each type is being held throughout the economy at large.

DIRECTION OF THE U.S. BIOECONOMY

This section reviews the current status and growth of the bioeconomy by examining indicators of activity in many of its sectors. Given the multiple challenges of measuring the bioeconomy, an approach that relies not on a single indicator but on a range of metrics that capture the varied aspects of the bioeconomy is warranted. Our analysis relies whenever possible on public data sources, ideally those published by federal agencies, such as the U.S. Census Bureau or the U.S. National Science Foundation (NSF), and international organizations, such as the Organisation for Economic Co-operation and Development. In some cases, we relied on data collected by private organizations. A complete analysis of the full range of data available for measuring all of the subsectors of the bioeconomy would be ideal, but this would require a dedicated staff of independent researchers. Also included in the bioeconomy, as described earlier in this chapter, are the social benefits of the bioeconomy's contribution to human and environmental health. Measurement of these benefits, also a complex job, is not included in this chapter's analysis.

National Investments in the Bioeconomy

NSF collects data on R&D funded and performed by U.S. government agencies, federally funded research and development centers (FFRDCs), state governments, academic institutions, nonprofit institutions, and businesses. This information is collected in separate surveys of federal government agencies, of state governments, of institutions of higher education (the Higher Education Research and Development [HERD] survey), and of businesses (the Business Research and Development Survey). A new survey of nonprofit institutions would be useful for studying developments in R&D funded and performed by these institutions in the near future.[35]

[35]Also, the business survey has been redesigned and renamed the Annual Business Survey. The new survey, which is forthcoming as of this writing, will focus on for-profit, nonfarm U.S. businesses with one or more employees, beginning with the data year 2017.

Consistent with the vision expounded by Vannevar Bush in his 1945 Letter to President Roosevelt, "Science the Endless Frontier," the U.S. government devotes the majority of its nonmilitary R&D investments to basic and applied scientific research, including research at universities. Business spending is devoted predominantly to product development (Arora et al., 2019; Bush, 1945). Summarizing R&D trends in the bioeconomy using federal data is challenging, as measures are broadly characterized by discipline and subfield. The most widely used subaggregate within total federal and university R&D spending is "life sciences," which includes as major subcategories biological and medical sciences (bioengineering and biomedical engineering data are not measured). Data on business R&D spending are collected by industry. NSF's survey also asks respondents to classify their spending according to "technology focus," one such focus being biotechnology. This allows industry-level R&D spending and performance to be cross-classified by focus field.[36] Unfortunately, the statistics on biotechnology are not regularly compiled for purposes of science policy analysis, nor are they reviewed in the biannual publication of the National Science Board, *Science and Engineering Indicators* (S&E).

Before reviewing these sources of information on R&D investments in the bioeconomy, the past decade of funding for the major *performers* of R&D (by size) in the United States in the business and higher-education sectors were considered. This was based on the most recent data available for the period 2006 to 2016. Over this period, as seen in Figure 3-5, business enterprise expenditures on R&D (BERD) became increasingly important to American innovation, but federal funding flagged. Higher-education expenditures on R&D (HERD) were slightly down, reflecting mainly the impact of a decline in federal funding. Taken together, total U.S. R&D, public and private (which includes some small components not shown in Figure 3-5), moved roughly sideways relative to GDP during this period.

Federal Investments in the Bioeconomy

Data on federal funding for research are available by major discipline and are presented as a share of GDP in Figure 3-6. Research in the life sciences commands greater resources than that in any other major discipline. Spending on life sciences research peaked during the NIH "doubling" of the early 2000s, reaching nearly 0.25 percent of GDP. That spending has declined to under 0.2 percent of GDP since. All told, total federal funding for R&D (which includes development funds not shown in Figure 3-6) has

[36]In addition to biotechnology, the other cross-cutting technologies that are surveyed are software, energy, environment, and nanotechnology.

FIGURE 3-5 Expenditures on R&D in the business and higher-education sectors and federal R&D funding (2006, 2011, 2016). NOTES: BERD and HERD = expenditures on R&D by the business and higher-education sectors, respectively; they include funds supplied by the federal government. HERD and federal funding encompass science and engineering fields only. Some federal R&D funds are dedicated to HERD. SOURCES: Gross domestic product (GDP) figures are from the Bureau of Economic Analysis, the National Economic Accounts, GDP, https://www.bea.gov/national (accessed July 20, 2019); R&D figures are from the National Science Foundation, the National Center for Science and Engineering Statistics, various surveys.

declined as a share of GDP since 1970, despite an increase in life sciences and multiple actions (e.g., the America Competes Acts in the 2000s) taken to raise U.S. competitiveness in the physical sciences and engineering.

Within the life sciences, research based in biology (other than environmental biology) doubled in real terms between 1999 and 2003 (see Figure 3-7). Although the amount of federal funds dedicated to biology research declined immediately thereafter, it has hovered at about $17 billion (in 2019 dollars, i.e., in real terms) in the dozen years since. NIH is the largest funder of R&D in the life sciences by a wide margin (see Figure 3-7), but funding for biological R&D is also a consequential share of R&D funding by other agencies (NSB and NSF, 2018).

Federal funding for bioengineering and biomedical engineering R&D is not typically grouped with the life science funding measures regularly analyzed in the biannual S&E. Rather, that funding is included in engineering R&D, with the consequence that typical federal spending indicators are not as comprehensive as is necessary to fully analyze federally

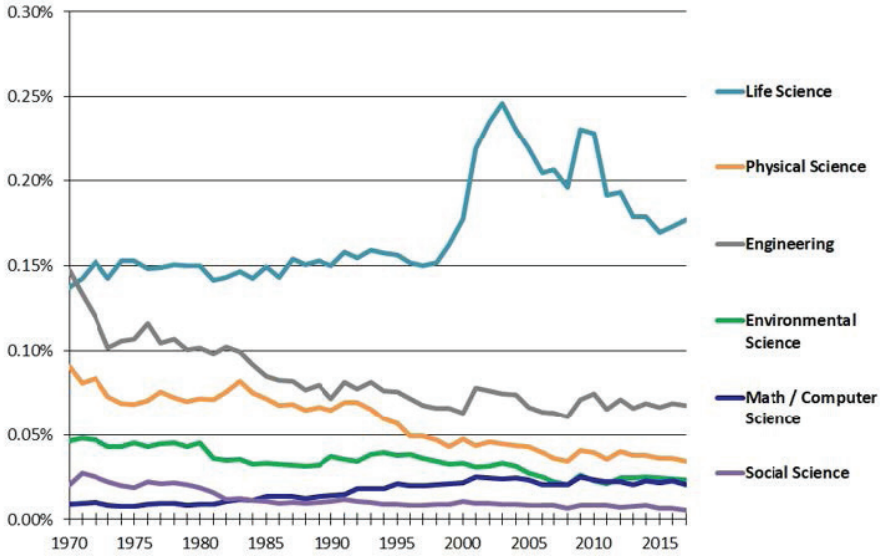


FIGURE 3-6 Federal research funding by discipline as a share of GDP, 1970–2017. SOURCES: National Science Foundation, Federal Funds for Research and Development series. Gross domestic product figures are from the Office of Management and Budget. Reprinted with permission from the American Association for the Advancement of Science (AAAS, 2019).

financed research in support of the bioeconomy. Certain detailed tables in the federal survey enable compilation of the appropriate statistics, and the desirability of doing this is seen by triangulating historical statistics reported in the HERD survey.[37] The S&E reports time-series data for federally financed HERD in engineering subfields, including expenditures for bioengineering and biomedical engineering. Although these expenditures are very small relative to total federally funded life sciences R&D (about 3 percent in 2016 and 2017) and would not include similarly classified intramural research at federal agencies or FFRDCs, federal support for academic research in this area has grown rapidly (8.5 percent per year from 2007 to 2017).[38] This category of federally funded R&D

[37]The committee thanks the National Center for Science and Engineering Statistics staff for suggesting this triangulation.

[38]Compare this with the following: federally financed academic life sciences R&D grew 2.2 percent annually from 2007 to 2017, federally financed academic biological and biomedical sciences R&D grew 2.8 percent annually, and nominal U.S. GDP grew 3.0 percent annually.

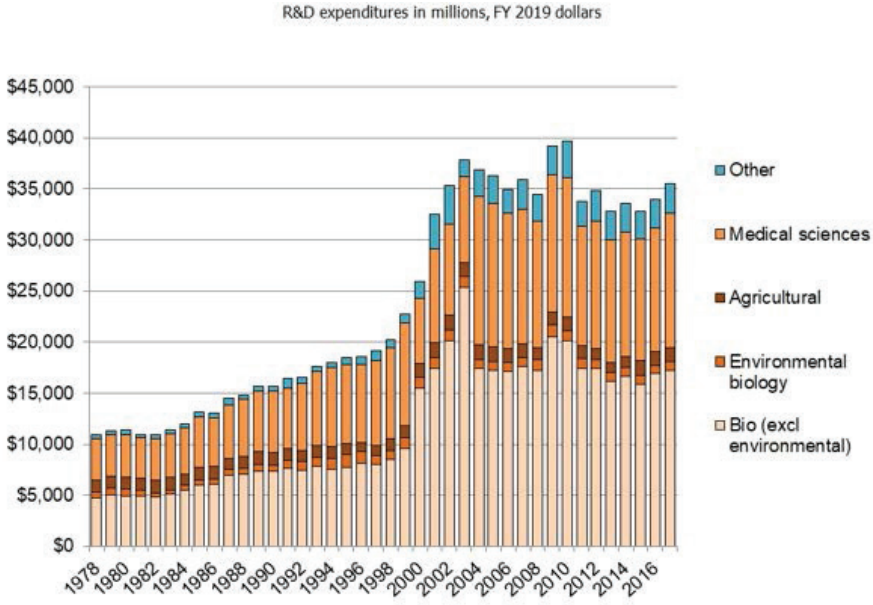


FIGURE 3-7 Life sciences research funding, 1978–2017. SOURCES: National Science Foundation, National Center for Science and Engineering Statistics, Federal Funds for R&D series. Reprinted with permission from the American Association for the Advancement of Science (AAAS, 2019).

performance at higher-education institutions posted the fastest growth among all detailed S&E categories reported in the HERD survey over this 10-year period.

The trends in federal versus other sources of bioeconomy R&D expenditures at institutions of higher education are summarized in Figure 3-8. Other funding sources include own-institution funds, states, businesses, and nonprofit institutions, with own-institution funds making up a bit more than half of total nonfederal sources in recent years. The slight downtrend in overall federal funding relative to nominal GDP is more than compensated for by an increase in funds from other sources.

R&D Investments in the Bioeconomy by Private Business

U.S. R&D investments have been fairly stable relative to U.S. GDP. Within total spending, that by the private business sector has increased in recent years. Three broad groupings of private business R&D investments in the U.S. economy are shown in Figure 3-9: (1) national accounts'

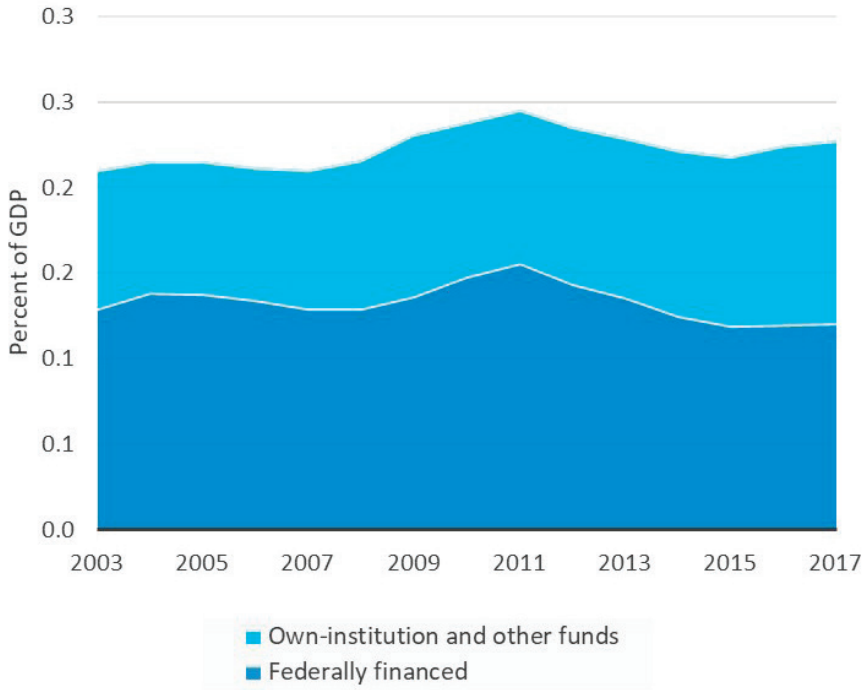


FIGURE 3-8 R&D expenditures in life sciences, bioengineering, and biomedical engineering by institutions of higher education. SOURCE: National Center for Science and Engineering Statistics (NCSES), higher-education expenditure on R&D surveys.

identifiable bioeconomy (including pharmaceuticals), (2) digital- and Internet-related (labeled "digital"), and (3) all other (labeled "other"). U.S. R&D in pharmaceuticals is shown separately (and labeled "pharma").

Business R&D in biotechnology and bioengineering cannot be wholly identified in national accounts data; despite this gap, however (and the need to remedy it), the trends shown in Figure 3-9 are generally indicative of developments in business R&D investments in the U.S. economy over the past 50 years. R&D in all things digital has climbed steadily in relation to GDP over the 50 years shown. Software development is a driver of the recent strength in this area and reflects, at least in part, investments in cyber protection and AI. R&D in pharmaceuticals also rose relative to GDP over time, dipping after 2008 and partially recovering thereafter. Identifiable R&D in the bioeconomy other than pharma (the difference

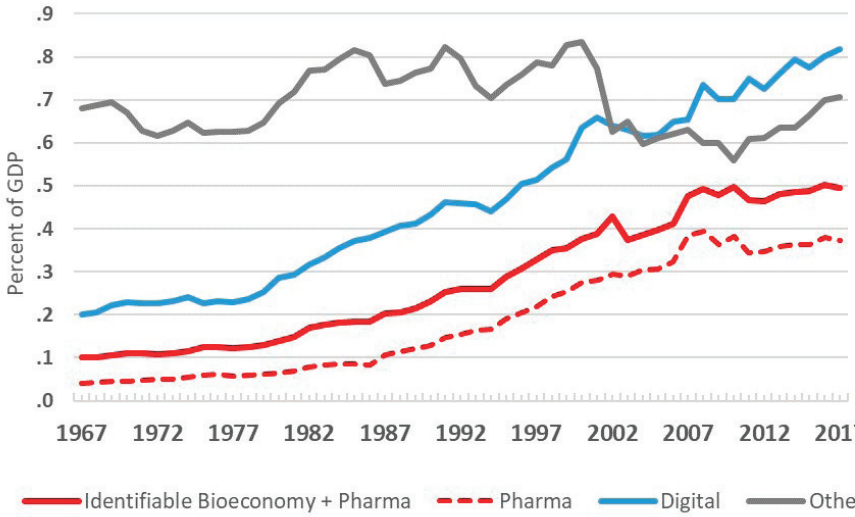


FIGURE 3-9 Business R&D investment by broad identifiable category, 1967–2017. NOTES: "Identifiable bioeconomy" includes Economic Research Service (ERS) tabulations of R&D in food and food inputs and estimates of R&D in biotechnology R&D services and medical instruments as evident in the U.S. national accounts' industry data on R&D. "Digital" includes R&D in the electronics products manufacturing, software publishing, and telecommunications services industries, plus software product development in all other industries. SOURCE: U.S. National Income and Product Accounts, ERS, National Center for Science and Engineering Statistics.

between the solid and red dashed lines in the figure) compensates for some of the weakness in pharma between 2008 and 2011. R&D in other industries turns sharply upward after 2008, reflecting a pickup in R&D investments in motor vehicles and a surge in "other nonmanufacturing" R&D expenditures in the professional and technical services industry (other than scientific R&D services). The latter development raises several questions, some of which are addressed in the remainder of this section.

Where Is the Bioeconomy? (Private Bioeconomy Activity Within Economic Sectors)

As described earlier in the section on measuring the bioeconomy, private economic activity that is supported by the bioeconomy covers bioindustrial materials, biopharmaceuticals, biobased consumer products,

agriculture, and bioeconomy-specialized equipment design and production. Private R&D expenditures supporting new product developments in these areas are difficult to identify in data collected and organized by industry, but as previously noted, NSF's surveys of business R&D have (since the early 2000s) included a question that asks respondents to identify expenditures whose technological focus is biology. These cross-cutting industry data on biotechnology R&D are not regularly compiled as time series for purposes of economic or science policy analysis. While such data would not capture R&D in medical equipment design, private expenditures on biotechnology R&D should be generally indicative of how biological sciences are driving some of the technological developments in the U.S. economy.

Figure 3-10 and Table 3-4 provide snapshots of U.S. biotechnology R&D expenditures compiled for this report. Figure 3-10 documents the increasing importance of biotechnology R&D relative to total business R&D and to total pharmaceutical R&D for 2005, 2011, and 2016. Between 2005 and 2016, the biotechnology fraction of R&D in pharmaceuticals increased, as did the overall ratio of biotechnology R&D to total R&D

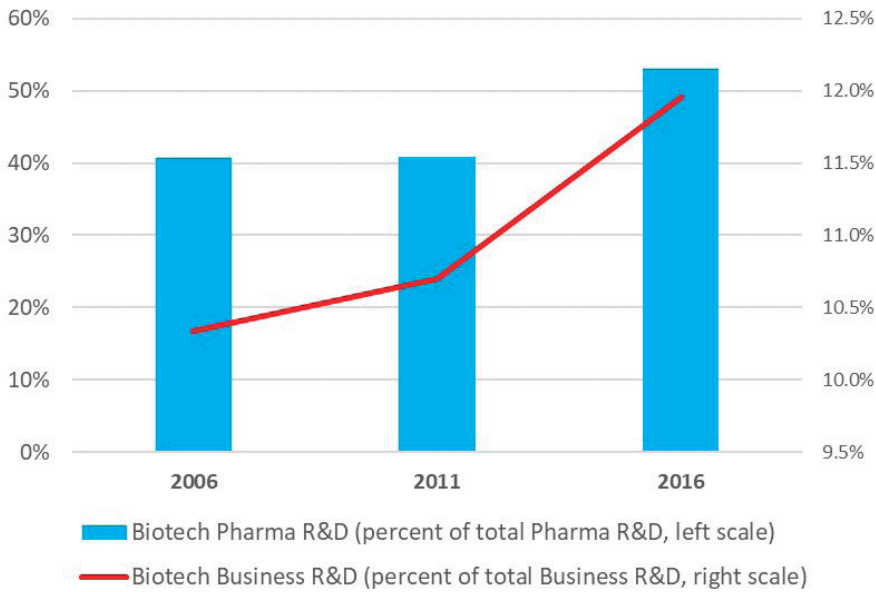


FIGURE 3-10 Business biotechnology R&D (2006, 2011, 2016). NOTE: Biotechnology R&D figures for 2006 are estimates based on published figures for 2005 and 2008. SOURCES: National Science Foundation, National Center for Science and Engineering Statistics, and U.S. Census Bureau, Business R&D and Innovation Survey, various years.

TABLE 3-4 U.S.-Based Companies, Represented by NAICS Codes, Conducting Biotechnology R&D, as a Function of Total Domestic R&D, Selected Segments, Selected Years (US$ millions)

	2016		
Segment (NAICS code)	Biotechnology R&D	Domestic R&D (in segment)	Biotech R&D/ Domestic R&D (by segment) (%)
All industries (21–23, 31–33, 42–81)	44,793	374,685	12.0
Manufacturing industries (31–33)	40,839	250,553	16.3
Nonmanufacturing industries (21–23, 42–81)	3,954	124,132	3.2
Specific industry (NAICS code)			
Food (311)	474	4,828	9.8
Basic chemicals (3251)	397	2,545	15.6
Pharmaceuticals and medicines (3254)	34,251	64,628	53.0
Other chemicals (other 325)	629	6,402	9.8
Plastics and rubber products (326)	282	3,752	7.5
Computer and electronic products (334)	3,230	77,385	4.2
Semiconductor & other elec. components (33344)	1,245	31,381	4.0
Professional, scientific, & technical services (54)	3,284	37,595	8.7
Scientific R&D services (5417)	3,013	14,842	20.3
Biotechnology R&D (541711)	2,283	4,464	51.1
Other scientific R&D (other 5417)	730	10,378	7.0
Health care services (621–623)	423	848	49.9

NOTES: NAICS = 2012 North American Industry Classification System; the table shows company performance of R&D regardless of the source of funds (e.g., own funds, government funds). The R&D in this table is the industrial R&D performed within company facilities, funded by all sources. The funds are the company's own; funds from outside organizations, such as other companies, research institutions, universities and colleges, nonprofit organizations, and state governments; and funds from the federal government.
SOURCES: National Science Foundation, National Center for Science and Engineering Statistics, and U.S. Census Bureau, Business R&D and Innovation Survey, 2016 and 2011, and Survey of Industrial Research and Development, 2005.

across all industries. The increase in biotechnology R&D over the years shown exceeds the increase in biotechnology pharma; the increase from 2006 to 2011 was buttressed by an increase in biotechnology R&D in the food products industry.

Table 3-4 shows industry detail behind the figures for 2016. Biotechnology R&D is concentrated in but not limited to the pharmaceutical and biotechnology R&D services industries. R&D with a biotechnology focus constituted more than 50 percent of total R&D in these two industries in 2016, but the biotechnology shares of R&D in the food, basic chemicals, other chemicals, other scientific R&D services, and heath care industries also are consequential.

It is important to note that, while biotechnology R&D conducted by the private sector is rising, the fraction of biotechnology R&D paid for by firms and paid for by others varies across business sector. These differences are highlighted in Table 3-5, which reports the fraction of U.S. biotechnology R&D conducted by firms that is paid for by the firms themselves compared with paid for by others. Overall, nearly 20 percent of funding for biotechnology R&D derives from sources other than the firm itself. Whereas most of the funding for biotechnology R&D in food and plastics is contributed by firms themselves, more than two-thirds of the funding in basic chemicals and just over three-fourths of payments to firms that provide specialized biotechnology R&D services derives from organizations other than the companies themselves, primarily the federal government.

Entrepreneurship and the Bioeconomy: Synthetic Biology as a Case Analysis

The data reviewed in the previous section suggest a robust rate of growth in R&D in bioengineering and biomedical engineering at institutions of higher education, but they are not dispositive regarding growth in business biotechnology R&D outside of pharmaceuticals. Nonetheless, in the broader picture, other sources suggest that a number of areas within the bioeconomy are experiencing investment and have the potential for accelerating its economic and social impacts. One of these areas is synthetic biology, for which analysis can be conducted using indicators that focus on entrepreneurship. A case analysis of synthetic biology follows.

Synthetic biology "collectively refers to concepts, approaches, and tools that enable the modification or creation of biological organisms" (NASEM, 2018, p. 1). The targeted manipulation of these components of life has been enabled by a series of advances in several scientific fields, including chemistry, engineering, and computer science, as well as biology. Taken together,

TABLE 3-5 Sources of Funding for Business Biotechnology R&D Expenditures, 2016

Segment (NAICS code)	Fraction of Biotechnology R&D Paid for by Company (%)	Fraction of Biotechnology R&D Paid for by Others (%)
All industries	82.5	17.5
Manufacturing industries	86.5	13.5
Food (311)	95.8	4.2
Basic chemicals (3251)	33.2	66.8
Pharmaceuticals and medicines (3254)	86.2	13.8
Other chemicals (other 325)	81.4	18.6
Plastics and rubber products (326)	100.0	0.0
Computer and electronic products (334)	87.8	12.2
Professional, scientific, and technical services (54)	30.9	69.1
Scientific R&D services (5417)	27.6	72.4
Biotechnology R&D (541711)	23.7	76.3
Other scientific R&D (other 5417)	39.9	60.1
Health care services (621–623)	93.6	6.4

NOTES: NAICS = North American Industry Classification System. Indented categories are subsets of the NAICS codes above them. For example, "Biotechnology R&D (541711)" and "Other scientific R&D (other 5417)" are both subsets of "Scientific R&D services (5417)," which is in turn a subset of "Professional, scientific, and technical services (54)."
SOURCES: National Science Foundation, National Center for Science and Engineering Statistics, and U.S. Census Bureau, Business R&D and Innovation Survey, 2016.

these advances have created a set of tools that can be used to analyze, model, and design organisms that have specific, valuable functions or address particular problems.

The goal of adapting the biological features of microbes, plants, and animals to serve human purposes is not new. Indeed, through the use of selective breeding, humans have been manipulating the genetic stock of the plant and animal world for millennia. The difference with synthetic biology is that these tools can now be deployed to affect, rapidly and vastly, enzymes, biological systems, and entire organisms.

Synthetic biology has fully emerged as a scientific field and is now offered as an area of study in biology along with biophysics, pharmacology, and systems biology at leading universities, including the University of California, Berkeley; Harvard University; and the Massachusetts Institute of Technology. One of the key features of synthetic biology is that its potential to engineer living organisms not only is an important driver of fundamental research but also (through the functions and synthesized products of these organisms) has direct relevance for immediate commercial application.

This positioning has enabled synthetic biology to become not just a rich field of scientific endeavor but a ripe area for entrepreneurship as well. In the report *Tracking the Growth of Synthetic Biology* (Wilson Center, 2013), the Wilson Center at Princeton University identifies 508 new facilities conducting research in synthetic biology between 2009 and 2013, 131 of which were new business entities. These facilities were conducting application-oriented work in a variety of areas, including medicines; specialty/fine chemicals; fuels and fuel additives; plastics, polymers, and rubbers; plant feedstocks; nutrients; waste management and pathogen detection/control; dispersants for use in oil spill cleanups; mining; and aquaculture. (Note that this period largely predated the discovery of and subsequent explosion in the application of clustered regularly interspaced short palindromic repeats gene-editing techniques.) Since then, multiple accelerators have emerged that specialize in synthetic biology, including IndieBio in San Francisco and Syndicated at Imperial College London.

SynBioBeta, an organization devoted to supporting research and commercialization in synthetic biology, organizes conferences; develops partnerships; circulates information; and creates ways for researchers, funders, and partners to interact and identify scientific, technical, and business opportunities. SynBioBeta also tracks the number of synthetic biology companies formed and the amount of funding they receive. In 2000, it identified 62 entrepreneurial ventures in synthetic biology, and it subsequently identified an increasing number of start-ups each year, including 579 such start-ups in 2018 (see Figure 3-11). According to SynBioBeta data, funding for synthetic biology companies had risen from less than $250 million in 2009 to $1 billion by 2015, and increased nearly fourfold thereafter to $3.8 billion in 2018 (see Figure 3-12). The two largest fundraisers in 2018 (see Figure 3-13) were Moderna Therapeutics, a Cambridge, Massachusetts–based firm that specializes in drug discovery research using messenger RNA, and Zymergen, an Emeryville, California–based firm that manufactures microbes for industrial use.

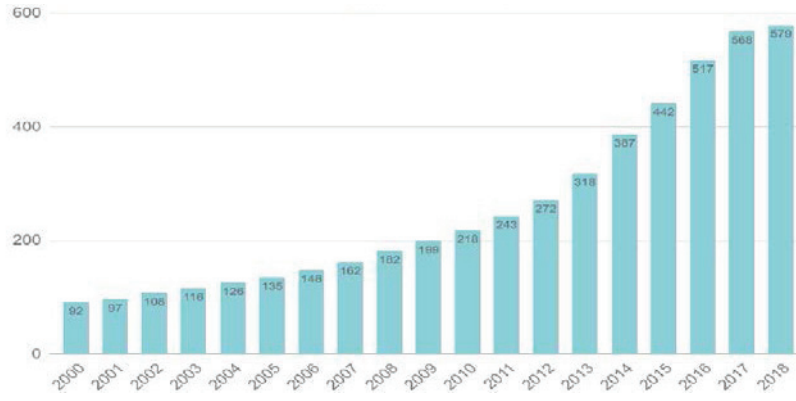


FIGURE 3-11 Synthetic biology start-ups, 2000–2018. SOURCE: Cumbers, 2019. Presentation to the committee January 28, 2019.

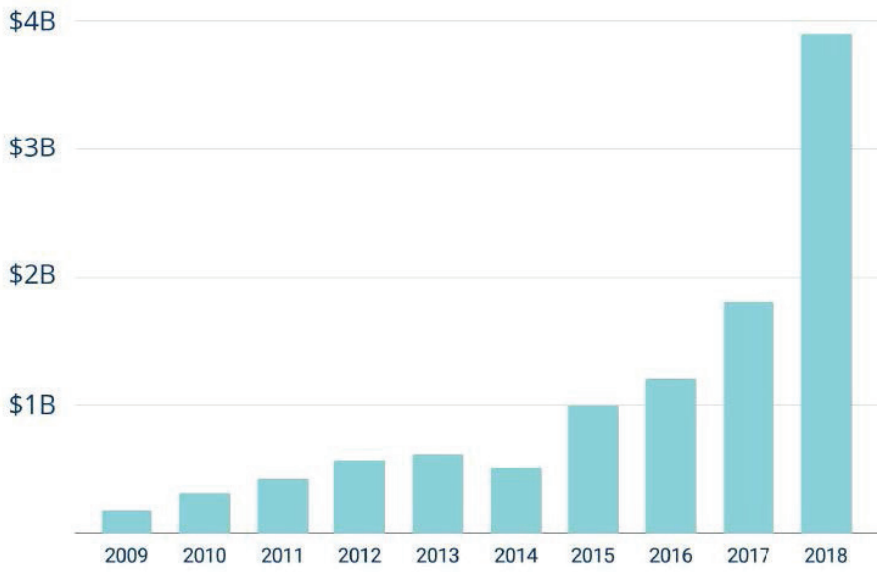


FIGURE 3-12 Funding for synthetic biology companies, 2009–2018. NOTE: 2018 ≅ $3.8 billion. SOURCE: Cumbers, 2019. Presentation to the committee January 28, 2019.

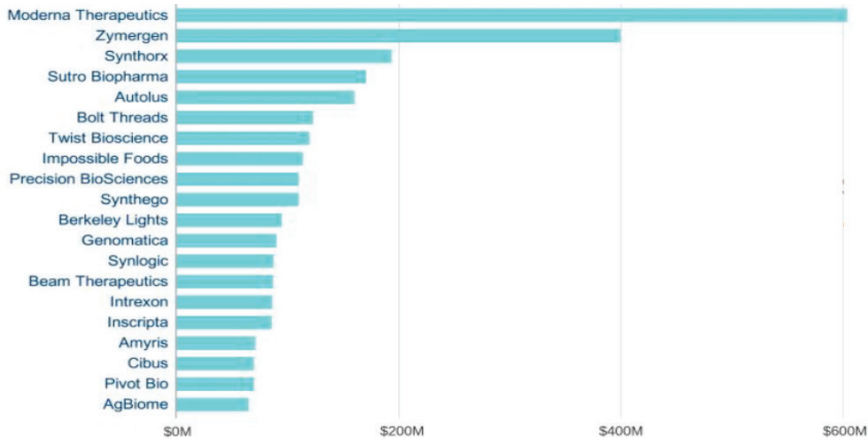


FIGURE 3-13 Top synthetic biology fundraisers, 2018. SOURCE: Cumbers, 2019. Presentation to the committee January 28, 2019.

The United States appears to be the world's leader in synthetic biology enterprises. This leadership is explored in greater detail later in the chapter. SynBioBeta estimates that there were more than 350 U.S.-based firms in this space in 2019. Like many other firms in the life sciences, these firms cluster in the regions around Boston and San Francisco, although there is also considerable geographic dispersion (see Figure 3-14). The Wilson Center (2013) report notes that facilities engaged in synthetic biology research or entrepreneurship existed in 40 of the 50 states as of 2013.

Private Bioeconomy Employment: Biotechnology Research and Development Services

Along with R&D expenditures and entrepreneurship, employment in the bioeconomy is a potentially valuable indicator of the extent and nature of its economic activity. These data are collected by industry and are often difficult to obtain. Employment data are both detailed and timely, however, and available by detailed geographies. Our analysis was focused on employment in the biotechnology R&D services industry as defined by the U.S. Bureau of Labor Statistics' Current Employment Statistics survey. Importantly, this is potentially an indicator that is correlated with overall bioeconomy employment, but it represents only a subset of the total bioeconomy workforce.

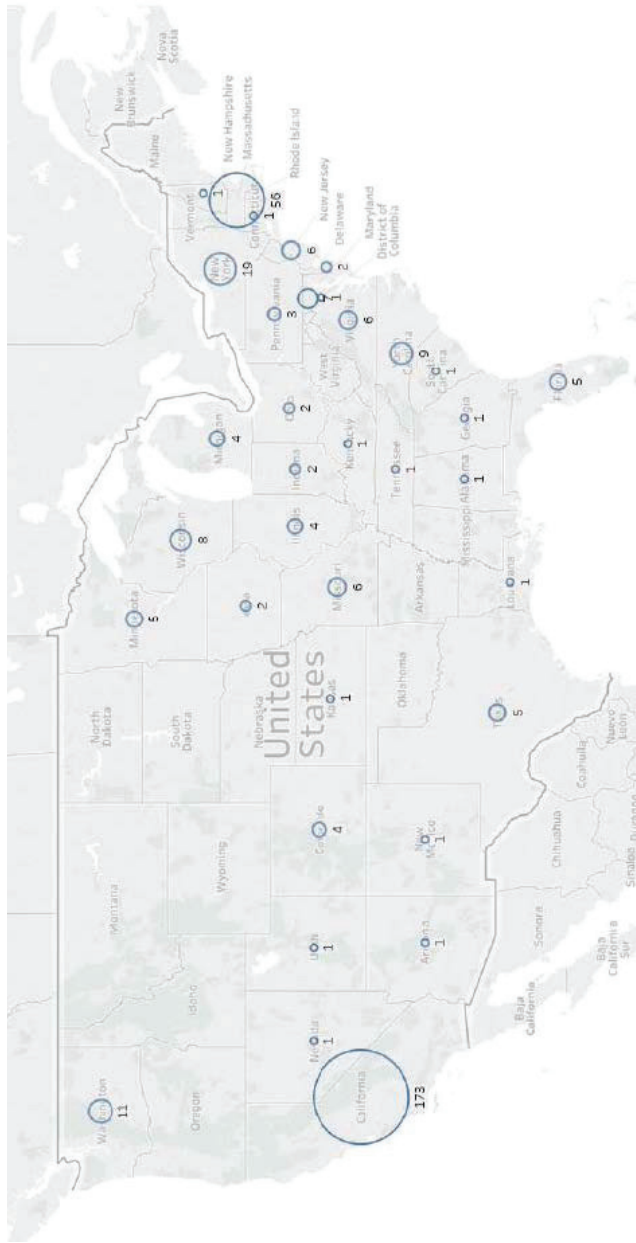


FIGURE 3-14 U.S. locations of synthetic biology firms. SOURCE: Cumbers, 2019. Presentation to the committee January 28, 2019.

Figure 3-15 presents historical data on the number of nonfarm employees overall and the number employed in biotechnology R&D services. The number of these workers was relatively stable at approximately 100,000 during the 1990s, but it had risen to more than 140,000 by 2008 and, after a modest decline during the Great Recession, has been rising dramatically since 2013, from around 140,000 to more than 200,000 in 2018. Overall (nonfarm) labor has been rising since the Great Recession, but since 2013 it has not increased at nearly the same rate as employment in the biotechnology R&D services industry.

Despite the substantial increase in the biotechnology R&D services workforce, real wages among these workers, like those of all private employees, have risen only somewhat consistently since 2006 (see Figure 3-16). The earnings of biotechnology R&D services workers are, however, nearly double those of other privately employed workers, although there is substantial variation in wages across U.S. regions (see Table 3-6).

A key feature of employment in biotechnology R&D services is that it is geographically concentrated (Feldman et al., 2015). Nearly 20 percent of all these jobs are concentrated in the Boston Metropolitan Statistical Area (MSA), and more than 50 percent are concentrated in the five largest MSAs—Boston, San Francisco, New York, San Diego, and Philadelphia. Altogether, the top 15 MSAs account for nearly 75 percent of the

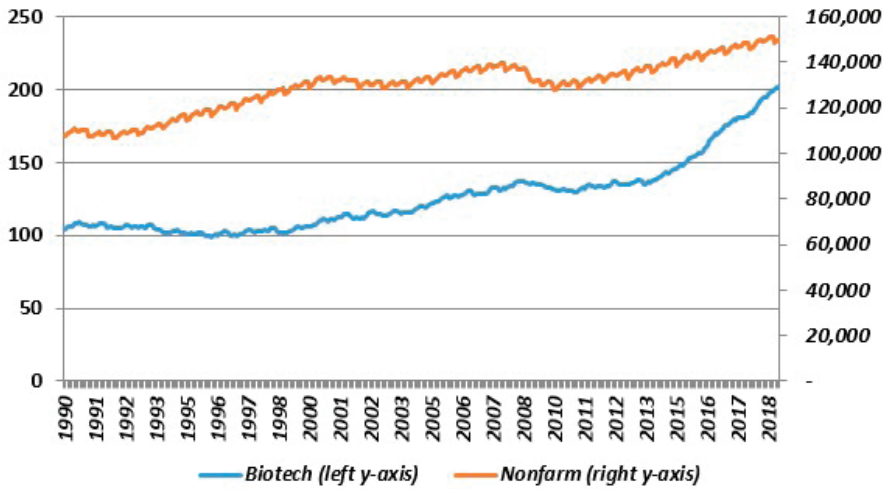


FIGURE 3-15 Thousands of employees, total nonfarm versus biotechnology R&D services, 1990–2019 (not seasonally adjusted, national). NOTE: "Biotech" data reflect employment in R&D biotechnology services except nanobiotechnology. SOURCE: U.S. Bureau of Labor Statistics (2019); data on Employment, Hours, and Earnings from the Current Employment Statistics survey.

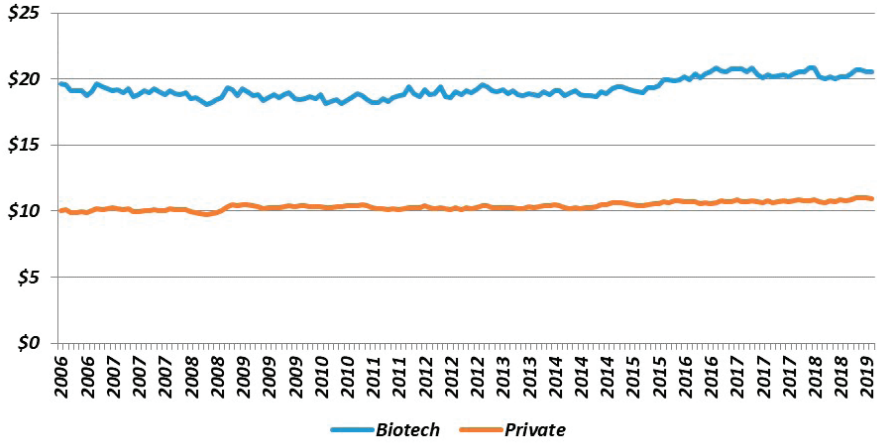


FIGURE 3-16 Average hourly earnings of all employees, 1982–1984 dollars, all private employees and biotechnology R&D services employees. SOURCE: U.S. Bureau of Labor Statistics (2019); data on Employment, Hours, and Earnings from the Current Employment Statistics survey.

biotechnology R&D services workforce; the remaining 25 percent is dispersed around the country. These figures may not, however, be representative of other segments of the biotechnology workforce (e.g., agricultural bioengineering), which may be less geographically concentrated.

Indicators of Bioeconomy Innovation Outcomes

Patents

Innovation studies have long viewed patents as an indicator of innovation, and as a result, the strengths and limitations of this approach are well understood (Hall et al., 2001; Machlup, 1961; Mansfield, 1986; Pakes and Griliches, 1980; Scherer, 1983). Pakes and Griliches (1980, p. 378) note that "patents are a flawed measure (of innovative output) particularly since not all new innovations are patented and since patents differ greatly in their economic impact." Furthermore, not all patents represent innovation.

Patents are typically leading indicators of innovation in industries in which they can be closely linked with particular scientific advances, such as new molecular entities, including the chemical and biopharmaceutical sectors (Henderson and Cockburn, 1996; Levin et al., 1987; Scherer, 1983). Scholars are generally cautious when interpreting measures based on

TABLE 3-6 Employment and Wages in Biotechnology R&D Services (Except Nanobiotechnology), U.S. National Totals and the 15 Metropolitan Statistical Areas Accounting for the Most Jobs (2017)

Metropolitan Statistical Area	Annual Average Employment		Total Annual Wages ($)	Annual Wages per Employee ($)	Percentage of Jobs	Cumulative Percentage
	Jobs	Rank				
U.S. TOTAL	179,666		29,815,414,623	165,949	100	
Boston-Cambridge-Newton, MA-NH	33,496	1	6,504,403,104	194,187	18.6	18.6
San Francisco-Oakland-Hayward, CA	18,023	2	4,006,327,159	222,287	10.0	28.7
New York-Newark-Jersey City, NY-NJ-PA	17,830	3	4,709,751,836	264,144	9.9	38.6
San Diego-Carlsbad, CA	14,477	4	2,076,041,842	143,403	8.1	46.7
Philadelphia-Camden-Wilmington, PA-NJ-DE-MD	13,164	5	2,217,477,645	168,447	7.3	54.0
Washington-Arlington-Alexandria, DC-VA-MD-WV	8,129	6	911,988,678	112,185	4.5	58.5
Baltimore-Columbia-Towson, MD	7,517	7	846,006,948	112,551	4.2	62.7
Seattle-Tacoma-Bellevue, WA	6,981	8	812,726,542	116,421	3.9	66.6
Durham-Chapel Hill, NC	2,700	9	355,531,356	131,678	1.5	68.1
Chicago-Naperville-Elgin, IL-IN-WI	2,426	10	407,640,479	168,065	1.4	69.4
San Jose-Sunnyvale-Santa Clara, CA	2,387	11	371,108,430	155,471	1.3	70.8
Raleigh, NC	2,128	12	301,049,281	141,504	1.2	71.9
Indianapolis-Carmel-Anderson, IN	1,778	13	225,105,395	126,588	1.0	72.9
Worcester, MA-CT	1,698	14	253,118,792	149,091	0.9	73.9
Dallas-Fort Worth-Arlington, TX	1,382	15	133,516,283	96,640	0.8	74.6

SOURCE: Quarterly Census of Employment and Wages, Bureau of Labor Statistics. Private, NAICS 541714 Research and development in biotechnology (except nanobiotechnology), All Metropolitan Statistical Areas 2017 Annual Averages, All establishment sizes. See https://data.bls.gov/cew/apps/data_views/data_views.htm#tab=Tables (accessed October 21, 2019).

patent levels, however, and recognize that substantial gaming is possible in the patent system (Jaffe and Lerner, 2004).[39]

A further challenge of using patents as indicators of bioeconomy innovation is that the value and meaning of such patents have changed over time. Patents remain the main currency of the pharmaceutical industry, as they provide specific protection for molecules approved by the U.S. Food and Drug Administration (FDA) for use in medicines, but their interpretation is different in other sectors of the bioeconomy. For example, the U.S. Supreme Court's 2013 decision in *Association for Molecular Pathology v. Myriad*[40] invalidated the use of patents for certain types of genetic materials. As a result, some firms in this space retreated from patent-focused strategies, while others continued an approach in which patenting played a key role in securing intellectual property rights.

A comprehensive analysis of the size of the bioeconomy would identify a series of patent classes consistent with definitions of the bioeconomy and compute their patent output, focusing primarily on changes in patenting over time. Such comparative, longitudinal analyses are more informative than point-in-time (cross-sectional) analyses, as they minimize the difficulties of interpreting what each patent means by focusing on relative rather than absolute levels of patenting. Analysis of global leadership in bioeconomy sectors is discussed in the Chapter 4.

New Biobased Products and Production Processes

Although optimism about the future outputs of biotechnology R&D is substantial (see, e.g., NASEM, 2017), evidence of strong growth in biotechnology outcomes is mixed. While pharmaceutical R&D appears to have experienced productivity declines in recent decades, the number of Biological License Applications for new biological drugs has increased, as have registrations to the U.S. Environmental Protection Agency (EPA) of products with microbial commercial activity. The number of gene clusters tested in submissions of products for field releases to USDA's Animal and Plant Inspection Service is also up (NASEM, 2017).

Findings of recent academic research on productivity in pharmaceuticals and biotechnology are mixed. Numerous authors suggest that pharmaceutical R&D is experiencing a productivity slowdown, despite advances in biotechnology and data-driven discovery efforts. For example, Pammolli and colleagues (2011) argue that productivity in pharmaceutical

[39]This subject is addressed in many studies and applications (e.g., Marco and Miller, 2019; the Innovation-alpha Stock Price Indexes developed by M-CAM), and is the impetus behind changes in processes undertaken by the U.S. Patent and Trademark Office (e.g., Graham et al., 2018).

[40]569 U.S. 576.

R&D has indeed been decreasing, and that the decrease is not simply a result of demand and competition but results, at least in part, from firms directing their R&D efforts toward complex therapeutic areas with a historically low likelihood of success. Gittelman (2016) suggests that a shift away from clinical research paradigms may have played a role in the slowdown. Cockburn (2006) is more optimistic about the data, noting that many pessimistic estimates account insufficiently for inflation in health care R&D costs and thus overestimate pharmaceutical R&D spending, resulting in an underestimate for productivity.

Other authors note that increases in the cost of pharmaceutical R&D are real, and that they reflect increasingly high costs of clinical testing, as well as rising costs of preclinical discovery (DiMasi et al., 2016). Specifically, they note that "aggregating across phases, we found an out-of-pocket clinical period cost per approved new drug estimate of $965 million and a capitalized clinical period cost per approved new drug estimate of $1,460 million. In constant dollars, these costs are 2.6 and 2.4 times higher than those we found in our previous study, respectively" (DiMasi et al., 2016, p. 25).

Overall, pharma performance measured in terms of new molecular entities and the productivity of global R&D spending in these terms has not been encouraging, despite decades of optimism as a result of scientific breakthroughs (see Figures 3-17 and 3-18).

Biotechnology-Based Pharma Versus Other Pharma (Except Diagnostics)

Firm sales and productivity in the bioeconomy are difficult economic concepts to measure, as economic data are typically focused on specific industries rather than on technological approaches within industry. However, insights can be gained about the bioeconomy by examining some detailed sales data collected by NSF *from R&D-performing firms only*. Figure 3-19 reports worldwide sales for U.S.-based firms in selected industries that engaged in or funded R&D. The data cover sales for firms in "pharmaceutical, medicinal, botanical, and biological products manufacturing (excluding diagnostics)," which are referred to here as "other" pharmaceuticals and plotted on the right-hand axis of the figure; sales of some other relevant groupings are shown on the left-hand axis. One notable feature of these data is that sales of other pharmaceuticals are an order of magnitude greater than those for the other groupings shown.

A second notable feature—one especially relevant to analyzing the bioeconomy—concerns the growth in sales of biotechnology-based pharma and biotechnology products (by R&D-performing firms). Data for this component begin in 2013, at $40 billion, and are more than double 4 years later (sales were $91 billion in 2016). This may augur hope relative

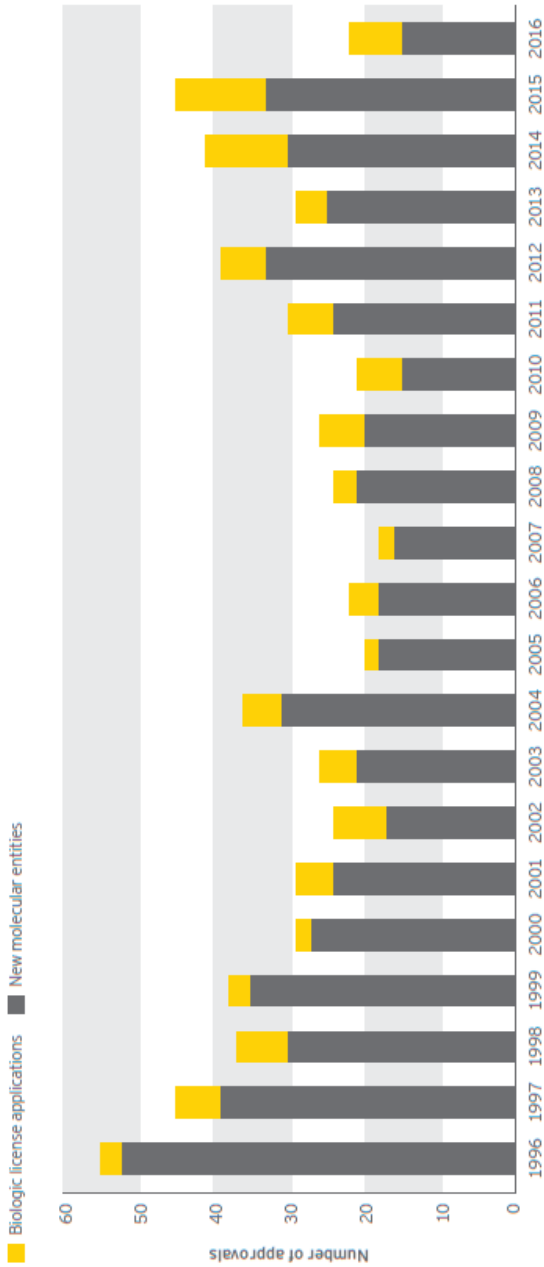


FIGURE 3-17 U.S. Food and Drug Administration (FDA) product approvals, 1996–2016. NOTE: U.S. product approvals are based only on approval by FDA's Center for Drug Evaluation and Research. SOURCE: EY and FDA. Reprinted with permission; copyright 2017, Ernst & Young LLP.

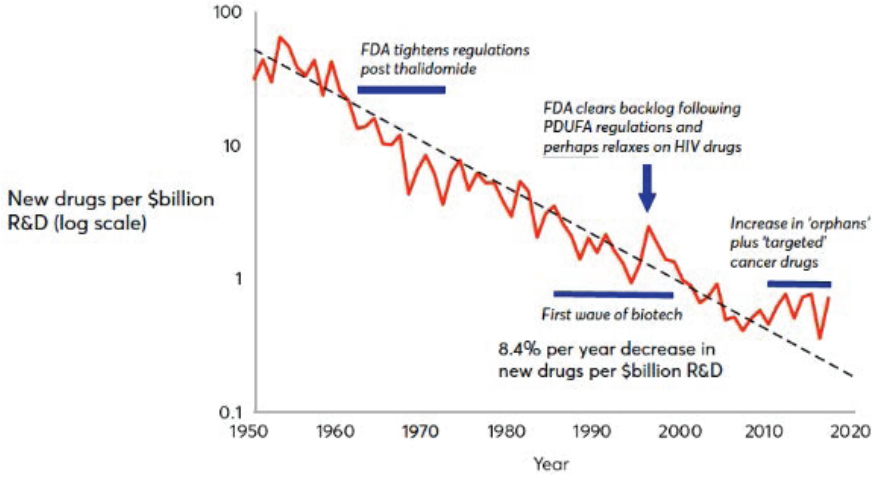


FIGURE 3-18 Eroom's law: The number of new molecules approved by the U.S. Food and Drug Administration (pharma and biotech) per US$ billion global R&D spending. NOTE: FDA = U.S. Food and Drug Administration; PDUFA = Prescription Drug User Fee Act. SOURCES: Jones and Wilsdon, 2018; Scannell et al., 2012.

to the challenges of drug discovery highlighted in the previous section. By contrast, sales of biotechnology research services (R&D-performing firms only) in 2016 were lower than they were 5 years earlier. Figure 3-19 replicates the prior figure, focusing on domestic sales by U.S.-based firms rather than worldwide sales; the patterns in these data are similar to those in the worldwide sales data. Domestic sales are 75 percent of worldwide sales for other pharmaceuticals and 85 percent for biotechnology-based pharmaceuticals and biotechnology products (see Figure 3-20). It is important to note that, while the change in the extent of sales of biotechnology-based products is substantial, the sales of such products are only a small fraction of the level of sales of pharmaceutical products that are not biotechnology based.

Other Innovation Outcomes and Outputs

Microbial commercial activity notices The Toxic Substances Control Act (TSCA) gives authority to EPA to review industrial platforms that employ biotechnology. EPA has published data on the applications it has received under TSCA up to June 2016. Figure 3-21 plots the number of Microbial Commercial Activity Notice submissions received by EPA by year of application for 1998–2015. The initial rate of these registrations was quite low, but they doubled in 2013 and 2014 relative to prior years and more than tripled in 2015 relative to 2013 or 2014, reaching 35 in 2015.

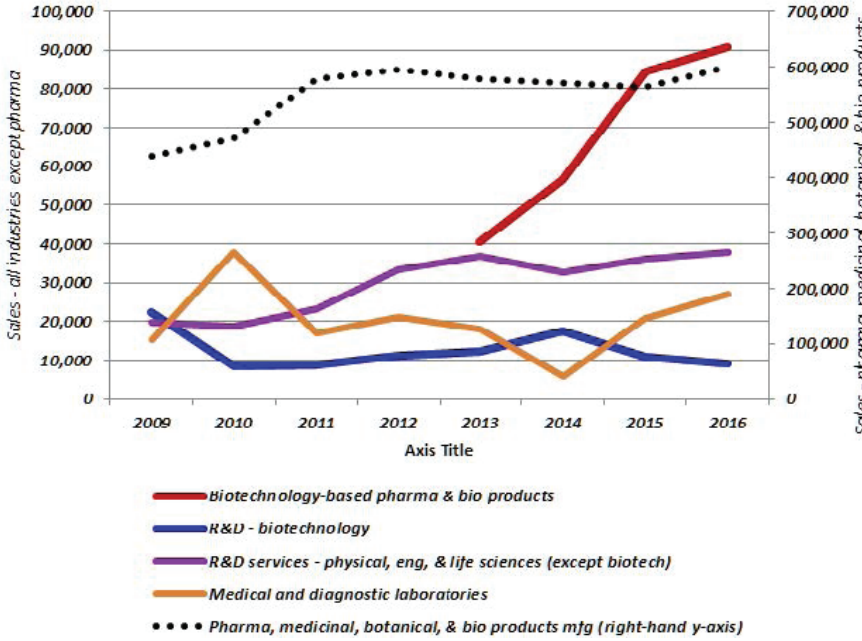


FIGURE 3-19 Worldwide sales for companies located in the United States that performed or funded R&D, by business activity: 2009–2016 (US$ millions, nominal). SOURCES: Business R&D and Innovation Survey, which is compiled based on data from the National Science Foundation, the National Center for Science and Engineering Statistics, and the U.S. Census Bureau (Table 74, available at https://ncses.nsf.gov/pubs/nsf18313/#data-tables& [accessed August 1, 2019]).

Agricultural outputs There are a number of perspectives on which agricultural products should be included in a definition of the bioeconomy. Most European agencies take a broad view, including such sectors as food, beverages, tobacco, and wood products that either produce or rely on biologically produced materials. In this report, those agricultural products derived from R&D in the life sciences are considered to be included in the bioeconomy. These would include, among others, corn, cotton, forestry products, and sugar products that fall under any of the four criteria described in Chapter 2. A detailed analysis of the nature of these products and estimates of their contributions to economic value can be found in reports on the economic impact of biobased products, including Daystar et al. (2018) and Golden et al. (2015). While such a detailed analysis exceeds the scope of this committee, we nevertheless present data on a number of key agricultural outputs (i.e., those related to GM crops).

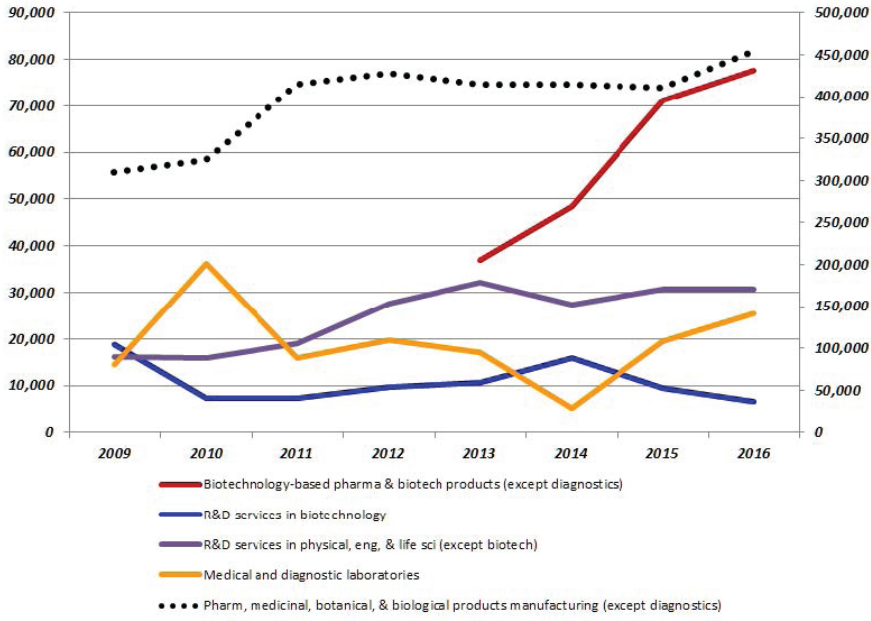


FIGURE 3-20 Domestic sales for companies located in the United States that performed or funded R&D, by business activity: 2009–2016 (US$ millions). NOTE: Pharma, medicinal, botanical, and biological products are on the right y-axis. SOURCES: Business R&D and Innovation Survey, which is compiled based on data from the National Science Foundation, the National Center for Science and Engineering Statistics, and the U.S. Census Bureau (Table 74, available at https://ncses.nsf.gov/pubs/nsf18313/#data-tables& [accessed August 1, 2019]).

Crop varieties can be genetically modified to be herbicide tolerant (HT), allowing fields to be sprayed with herbicides that kill weeds without damaging the crops. They have also been genetically modified through the insertion of genes from the soil microbe Bt (*Bacillus thuringiensis*), which generate several proteins that are toxic to certain insect pests. Corn, cotton, and soybean seed varieties with HT traits, Bt traits, or both (known as stacked varieties) first became commercially available in the mid-1990s. Direct data on sales values of GM crops are not regularly collected in the United States.

By 2018, more than 90 percent of corn, cotton, and soybean acreage in the United States had been planted with varieties with the HT trait, while more than 90 percent of corn and cotton acreage had been planted with varieties with the Bt trait (see Figure 3-22). Data for GM sugarbeets, alfalfa, and canola are not collected as frequently, but as of 2013, 95 percent of U.S. canola acres, 99 percent of sugarbeet acres, and 13 percent of alfalfa acres were planted with GM HT seed varieties.

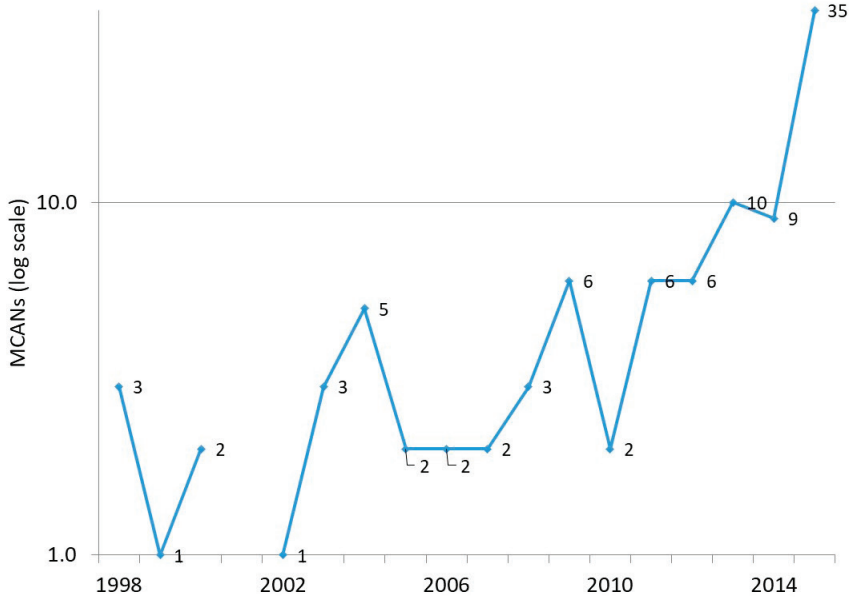


FIGURE 3-21 Microbial Commercial Activity Notices (MCAN), by year of application, 1998–2015. NOTE: Data are plotted on a log scale. SOURCE: 2018 EPA calculations using data posted at EPA.gov (accessed May 1, 2019).

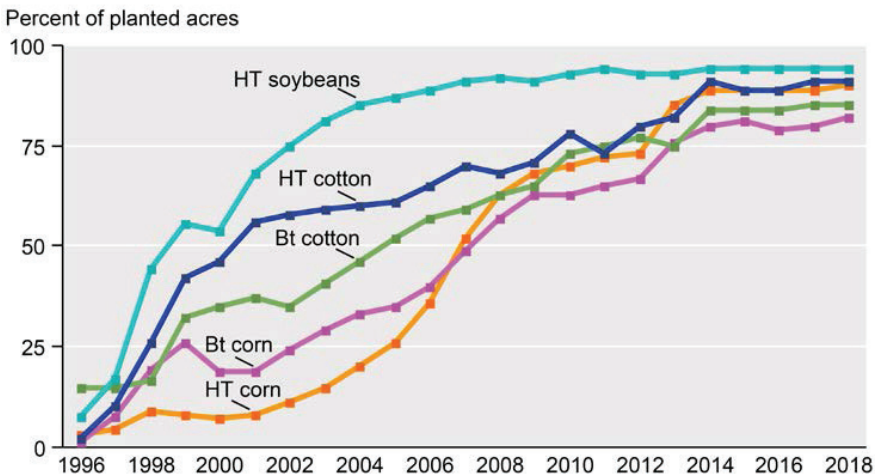


FIGURE 3-22 Fraction of planted acres, by genetically modified crop type, 1996–2018. NOTE: HT indicates herbicide-tolerant varieties; Bt indicates insect-resistant varieties (containing genes from the soil bacterium *Bacillus thuringiensis*). Data for each crop category include varieties with both HT and Bt (stacked) traits. SOURCE: USDA ERS, 2019.

USDA's Economic Research Service reports on the adoption of GM crops in the United States. Data for 2017 are presented in Table 3-7. Estimates for corn, soybeans, and cotton are for 2017, while those for alfalfa, sugarbeets, and canola are for 2013 (Fernandez-Cornejo et al., 2016). Data for crop sales come from USDA's 2017 *Census of Agriculture* (USDA NASS, 2017). In total, GM crops accounted for nearly half of the total sales value of all U.S. crops in 2017. Crops for which GM varieties are available accounted for 56 percent of total 2017 crop sales. Assuming that crop revenues are proportional to acreage, these data imply that GM crops accounted for nearly 48 percent of all U.S. crop revenues with more than $92 billion in sales in 2017.

Biofuels Biofuels represent an important alternative to fossil fuels. In the United States, the development of this sector has been encouraged by a series of policy initiatives. For example, the 2005 Energy Policy Act and 2007 Energy Independence and Security Act introduced a series of subsidies, tax credits, loans, direct grants, and standards intended to support R&D for biofuels, including ethanol, biodiesel, and cellulosic. By 2012, biofuels constituted more than 7 percent of total fuel consumption in the United States. Approximately 94 percent of the biofuel produced is ethanol (USDA ERS, n.d.). Figure 3-23 documents the rise in U.S. biofuel production between 2001 and 2017, during which time the production

TABLE 3-7 Sales, Acreage, and Value of Selected Genetically Modified (GM) Crops in the United States, 2017

Crops	Sales ($ billions)	Percentage of U.S. Crop Sales	Percentage of Acreage Planted to GM Crops	Imputed Percentage of U.S. Crop Sales from GM Crops	Imputed Gross Revenues from Sales of GM Crops (2017 $billions)
All U.S. crops	193.5				
Crops with commercially available GM seed varieties					
Corn	51.2	26.0	89.0	23.6	45.6
Soybeans	40.3	21.0	94.0	19.6	37.9
Cotton	6.7	3.0	91.0	3.1	6.1
Alfalfa	8.2	4.0	13.0	0.5	1.1
Sugarbeets	1.5	1.0	99.0	0.7	1.4
Canola	0.5	0.3	95.0	0.3	0.5
Subtotal, GM crops		**56.0**		**47.8**	**92.6**

SOURCES: Fernandez-Cornejo et al., 2016; USDA ERS, n.d., USDA NASS, 2017.

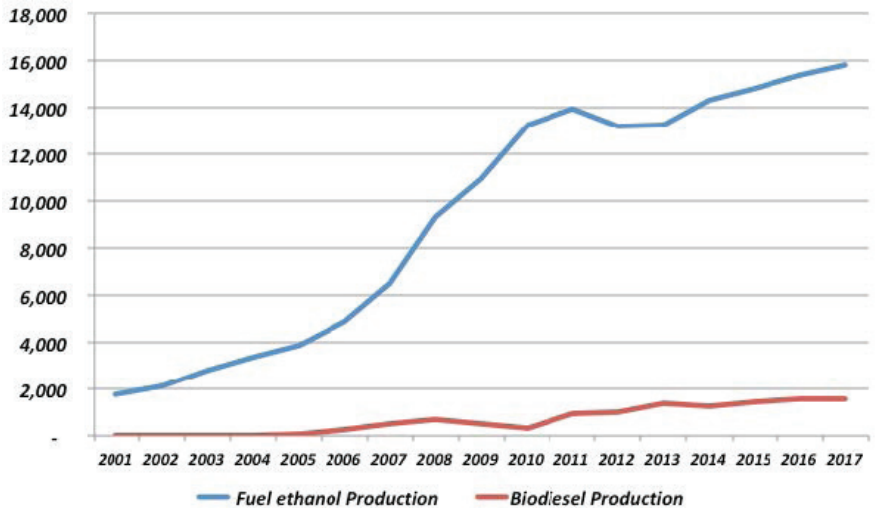


FIGURE 3-23 U.S. domestic biofuels production, millions of gallons, 2001–2017. SOURCE: USDA ERS, 2019.

of biofuel increased from slightly less than 2 billion gallons to nearly 16 billion gallons.

CONCLUSIONS

This chapter has reviewed the resources devoted by the United States to investments in the bioeconomy and examined how to measure the bioeconomy and assess its economic contributions to the larger U.S. economy. On the basis of this discussion, the committee arrived at the following conclusions.

Conclusion 3-1: The sector-specific aspects of the bioeconomy, its diffusion across industries, its potential for large societal benefits, its large science base and reliance on data-intensive research, the closeness of commercial innovation to a science base, and a high relative cost of commercial innovation make it difficult both to track the bioeconomy's contribution to the larger U.S. economy and to assess its prospects for future innovation.

Conclusion 3-2: A targeted and specialized framework for analyzing the bioeconomy's innovation ecosystem is needed—an approach that both looks broadly at investments in innovation (including investments in data and existing data analytic tools) and accounts

for all bioeconomy-specific new product investments (e.g., improvements in the efficiency of nondrug regulatory testing).

Conclusion 3-3: In some key areas, North American Industry Classification System code categories for economic sectors are currently too broad to capture activities within the bioeconomy accurately. In some cases (such as genetically modified crop production), practitioners have relied on secondary sources to augment aggregate sector data. Refining categorization of certain activities within broad categories of chemical manufacturing, research and development, and computer and electronic product manufacturing would facilitate future measurement of bioeconomy activities.

Conclusion 3-4: A satellite account system for the bioeconomy that includes the appropriate interindustry relationships for biobased production, a full articulation of the foreign versus domestic sources of supply for bioeconomy products, and a full accounting of the bioeconomy's intangible assets and databases (including ownership) is needed. If optimally designed to meet this need, the account would also, to the extent possible, incorporate quality-adjusted price deflators for bioeconomy products (e.g., biopharmaceuticals and biomedical equipment).

By applying its analysis of the available data gathered for this study, the committee carried out a pilot experiment to assess the various approaches for measuring the value of the bioeconomy.

Conclusion 3-5: The results of the committee's pilot valuation experiment are as follows: economic activity driven by the bioeconomy accounted for nearly 5.1 percent of the gross domestic product (GDP) in 2016 and could reach up to 7.4 percent if currently available biobased production processes were to completely displace nonbiological processes. This is a current guideline only because the panel's definition of the bioeconomy is meant to be "living."

Conclusion 3-6: The share of biobased materials and biotechnology-based products and production methods in the U.S. industrial sector has grown substantially in the past 15 years and is expected to continue to displace non-biobased materials and methods in the future. The continuation of biomedical breakthroughs, such as new drugs and targeted, yet broad, data-based medical solutions, will require continuing national investments in basic research and biological databases, as well as in the enablement of commercial innovation.

Annex 3-1
Studies of the Industrial Bioeconomy (Including Agriculture)

OVERVIEW OF THE LITERATURE

Several studies have taken a sector-based approach to defining and measuring the contribution of the industrial bioeconomy to a country's or region's overall economy. In these studies, economic activity within the bioeconomy is defined in terms of a country's system of national accounts, using North American Industry Classification System (NAICS) codes, in the United States and Canada; the European Union's (EU's) Nomenclature générale des Activités économiques dans les Communautés Européennes (NACE) codes; or United Nations input-output tables. One goal of these studies is often to measure the size of the bioeconomy in terms of the section's employment or gross value added relative to the larger economy. Another is to apply input-output modeling techniques to assess how sectors included in the bioeconomy interact with other sectors in the broader economy. However, a challenge is that the "bioeconomy cuts across sectors and therefore cannot be treated as a traditional sector in economics" (Wesseler and von Braun, 2017).

Expert researchers follow a two-step process. First, certain sectors are considered wholly within the bioeconomy (this approach may encode entire sectors within NAICS or NACE codes). Next, for remaining sectors, researchers assume either that all activities are considered outside the bioeconomy or that some are considered to have some subactivities within the bioeconomy, while others are designated as outside. For example, steel manufacturing would lie completely outside the bioeconomy, while electricity generation comprises biomass-generated electricity (within) and other generation (without).

A key problem is that NAICS and NACE codes often do not make a fine enough distinction within industries to separate components considered inside and outside of the bioeconomy definition. A common approach to addressing this limitation is to conduct industry surveys to determine which type of production within a sector may be "biobased." For example, plastics manufacturers may be surveyed to determine how much of their employment and production is devoted to bioplastics. This subset of bioplastic production would then be included as part of the bioeconomy.

EU economic policies are increasingly focused on a "circular economy," in which use of resources is maximized and waste is minimized, instead of a "linear economy," in which "take," "make," and "dispose" are primary elements. A circular economy employs a regenerative approach, including design for longevity, reuse, repair, and recycling as foundational elements. Not surprisingly, the term "circular bioeconomy" has gained traction in the European Union, and policies are being developed to maximize the use of biobased resources regarded as wastes (such as agricultural and forestry residues), with the long-term objective of gradually replacing fossil-based with biobased production (Philp and Winickoff, 2018).

Studies vary greatly in what sectors and activities within sectors are considered part of the bioeconomy, with distinct differences in particular between studies on North America and those on EU countries and Japan. EU studies tend to use relatively broad definitions, including sectors in their entirety that produce or fundamentally rely on biologically produced materials. For example, not only are primary sectors (agriculture, forestry, fisheries) included, but also food, beverage, tobacco, and wood products manufacturing. For other sectors, such as chemical manufacturing, researchers frequently conduct surveys to divide sectoral activity into biobased and other categories. In the United States and Canada, there has been a greater emphasis on applications of biotechnology, biological research and development (R&D), and substitution of biobased for fossil fuel–based products in manufacturing. Primary sectors (agriculture, forestry, and fisheries) are treated largely as outside the bioeconomy. Major exceptions are genetically modified (GM) crops and crops or trees grown specifically for energy production.

Lier and colleagues (2018) conducted a survey of EU government ministries tasked with monitoring bioeconomy performance or developing bioeconomy strategies. The survey asked respondents which NACE code activities were completely, partly, or not included in the bioeconomy sector. European ministries included primary sectors along with food, paper, and wood product manufacturing entirely. Only one study (by Ehrenfeld and Kropfhäußer, 2017) followed the approach of North American analyses, examining biological science R&D as part of the bioeconomy.

In general, North American studies do not include entire NAICS sectors in their definitions of bioeconomy sectors. They often rely on survey-based data collection within traditional sectors, focusing on novel technology applications to traditional sectors (e.g., GM crops), substitution of biobased for fossil fuel–based production (e.g., bioplastics), and biological R&D. In response, Carlson (2016) proposes three key additions to the NAICS system to improve its utility in delineating the size of the biotechnology sector (see Box 3-3 in the main chapter text).

Another approach input-output modelers have taken is to impute the contribution of the bioeconomy to other sectors. Researchers assume that the contribution of the bioeconomy to value added in a sector is proportional to the share of biologically produced inputs in that sector's production costs. So, for example, there would be virtually no bioeconomy value added derived from the steel sector, but a relatively large contribution from sectors using crop, fiber, and timber products. Efken and colleagues (2016) thus have a definition of the bioeconomy that extends to the retail grocery and restaurant sectors, arguing that "these industries only exist due to the fact that they process (picking and packing, preparing, offering) biological resources." The imputation approach avoids the need to conduct surveys of industries within NAICS or NACE codes. Instead, it relies on basic data from national input-output tables, with sectoral data reported similarly across countries. Using such an all-encompassing definition, however, means that quite traditional primary sectors, processing sectors, and service sectors that repackage and serve biologically derived goods account for the bulk of employment and value added attributable to the bioeconomy. This definition is far removed from one that focuses on novel biological technologies or even biobased substitution for fossil fuel–based production.

The estimates of the bioeconomy reported in Chapter 3 rely heavily on the studies of Carlson (2016, 2019) and Daystar et al. (2018). Therefore, those studies are reviewed in detail below.

CARLSON (2016, 2019)

Carlson (2016, 2019) collected data on gross sales revenues from industrial biobased activities. While his approach has the advantage of relying on data that "are publicly available at no cost or obtainable with minimal registration from sources on the Internet," some problems are entailed in comparing gross sales with the gross domestic product (GDP).[41] That said, Carlson's work, within its circumscribed boundary, is the most definitive to date.

[41]Gross sales are not the same as value added. Value added is the difference between gross output (sales) and intermediate inputs and represents the value of labor and capital used in producing gross output. The sum of value added across all industries is equal to GDP for the economy. In the United States, total gross sales are 1.7 times GDP. Carlson (2016) acknowledges the limitations of using gross sales, noting this approach "may include some double counting." In later work, Carlson (2019) attempts to correct this limitation; for example, corn used to produce biofuels is not double-counted. However, double-counting elsewhere in his estimates is still a problem. On the other hand, as noted in the main text of Chapter 3, studies that infer total economy effects via interindustry linkages produce larger impacts relative to isolating value added alone, and though imprecise, estimates based on gross output are closer to these broader-based estimates.

According to Carlson's estimates, U.S. genetically modified organism revenues were 2 percent of U.S. GDP in 2017 (see Figure Annex 3-1-1), about the same as 5 years earlier but up substantially since 2000, when the sector accounted for just 0.6 percent of GDP (Carlson, 2016, Table S1, 2019). Industrial biotechnology was the fastest-growing subcomponent of these estimates prior to 2012, and despite an unchanged ratio to GDP since then, within industrial biotechnology, revenues from biopharma ingredients have gained ground in relative terms (see Figure Annex 3-1-2).

Emerging R&D services are small in Carlson's estimates, about $2 billion. Official statistics from the U.S. Census Bureau for the biotechnology segment of the R&D services industry suggest that revenues in 2012 were much larger ($16.9 billion), but they were similar in that they reflect little evidence of growth.

In the U.S. Census Bureau statistics, revenues from R&D biotechnology services in 2012 were down slightly from the level reported in 2007 ($17.4 billion). This decline contrasts with R&D service revenues in other life sciences, which were $40.0 billion in 2012, up from $26.2 billion 5 years earlier. It is possible that genomics companies are in the latter category, or that a company such as Illumina, which sells sequencing machines as well as genomic services, is somewhere else entirely. The figures quoted are details from the 2012 economic census; detailed results from the 2017 economic census are not yet available. Annual product-level figures from the Census Bureau's Services Annual Survey do not report data for R&D services, much less components by type of R&D service.

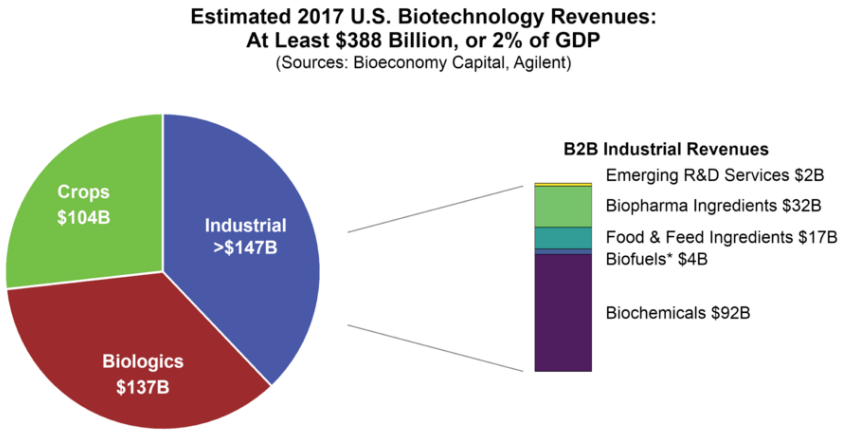


FIGURE ANNEX 3-1-1 Biotechnology revenues, 2017. NOTE: The cost of corn was removed from the biofuels revenues to avoid double-count in the crops segment. SOURCE: Bioeconomy Dashboard, available at http://bioeconomycapital.com/bioeconomy-dashboard (accessed April 10, 2019).

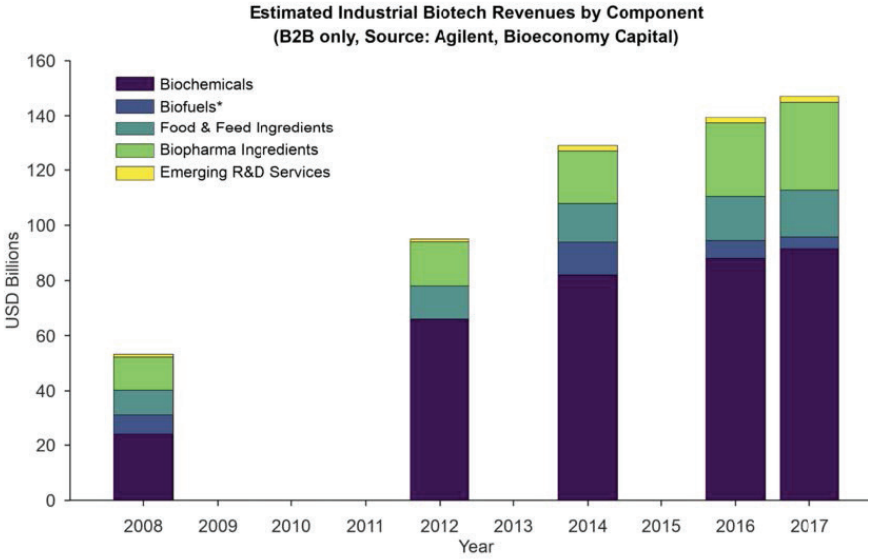


FIGURE ANNEX 3-1-2 Industrial biotechnology revenues by component. NOTE: The cost of corn was removed from the biofuels revenues to avoid double-count in the crops segment. SOURCE: Bioeconomy Dashboard, available at http://bioeconomycapital.com/bioeconomy-dashboard (accessed April 10, 2019).

Sales by R&D-performing firms within the R&D services industry are reviewed in the main text of Chapter 3.[42] The patterns in those data compare favorably with the comprehensive figures from the 2007 and 2012 economic censuses and with Carlson's estimates, suggesting the utility of a broader regular collection of the more timely annual revenue data for bioeconomy firms in the services industries. The National Science Foundation's (NSF's) data on sales are of course smaller than the U.S. Census Bureau's revenue data because not all firms in the R&D services industry conduct scientific R&D; the NSF data are 60 percent of U.S. Census Bureau revenues for biotechnology and 75 percent of revenues for the other life sciences segments in 2012. The downtrend in sales by R&D-performing firms in the biotechnology R&D services industry and increase in the other category of R&D services (which includes other physical sciences along with other life sciences) are evident in both surveys.[43] Carlson's

[42]Data available for download at https://ncses.nsf.gov/pubs/nsf18313/#data-tables&.

[43]Note also that the share of biotech revenues in 2012 by class of customer did not change materially between the two census years; that is, revenue from governments and nonprofits accounted for 10 percent of the total in each year, which suggests that the flagging performance of this segment is market driven.

estimates for "biopharma ingredients," while at a lower level because of the absence of manufacturers' markup, exhibit growth similar to that for sales by R&D-performing firms in biopharma. This result underscores the utility of Carlson's recommendation to segment product revenue data for the pharmaceutical industry along biotechnology/bioproduct lines.

Industrial biotechnology revenues in the Carlson system reflect business-to-business transactions and therefore understate the impact of biotechnology, because consumer biobased products (e.g., replacements for plastic wraps, biobased ink pens, personal genetic histories) are not necessarily captured. Consumer biobased products are one of the drivers of the synthetic biology start-up business segment of the bioeconomy discussed in the main chapter text. No studies or industry estimates assign a revenue figure to the consumer-driven portion of this activity, despite ample evidence of the importance of doing so. Consumer-oriented genomics companies (e.g., 23andMe), along with biobased consumer food companies (e.g., Impossible Foods), are becoming household names today.

DAYSTAR ET AL. (2018)

The U.S. Department of Agriculture commissioned the Daystar et al. (2018) report, the fourth in a series of reports tracking the impact of the biobased product industry on the U.S. economy. The sectors included in this report are

- agriculture and forestry,
- biobased chemicals,
- bioplastic bottles and packaging,
- biorefining (food),
- enzymes,
- forest products, and
- textiles.

The report specifically excludes the energy, livestock, feed, and pharmaceutical sectors.

Daystar and colleagues (2018) conducted an extensive input-output modeling exercise to trace biobased spending through the broader U.S. economy, including calculating economic multiplier effects. The report also examines environmental benefits; the economic impacts of biobased exports; and areas in which the use or manufacturing of biobased products could be more effective, including identifying technical and economic obstacles and recommending how those obstacles could be overcome.

In their analysis of environmental benefits, the authors endeavor to quantify how the production and use of biobased products reduce

greenhouse gas (GHG) emissions via displacement of petroleum-based products. They estimate that the petroleum saved by a 100 percent shift to biobased products (in the industries considered) would amount to as much as 9.4 million barrels of oil, based on 2016 data. In terms of reductions in GHG emissions, they estimate the reduction attributable to the biobased products industry to be as much as 12.7 million metric tons of carbon dioxide equivalent in 2016.

The strength of this study is in its methodology and its detailed coverage of certain biobased chemicals, enzymes, and biorefining of food. These areas encompass a complex and detailed set of products and processes that are difficult to identify in readily available data. For example, an area unearthed in the report's data is enzymes, specifically "other enzymes" identified as produced by NAICS 5 Digit Industry 32519—Other Basic Organic Chemical Manufacturing. This industry comprises establishments engaged primarily in manufacturing basic organic chemicals (except petrochemicals, industrial gases, and synthetic dyes and pigments) and includes enzyme proteins (i.e., basic synthetic chemicals), except those for pharmaceutical use.

In Daystar and colleagues' (2018) report, total enzymes also include biologics (NAICS 325414). The report estimates that total value added by the two enzyme subsectors rose dramatically in 2016, and that the combined type II multiplier for these subsectors is very large at 4.4 (see the stacked bar to the far right in Figure Annex 3-1-3).

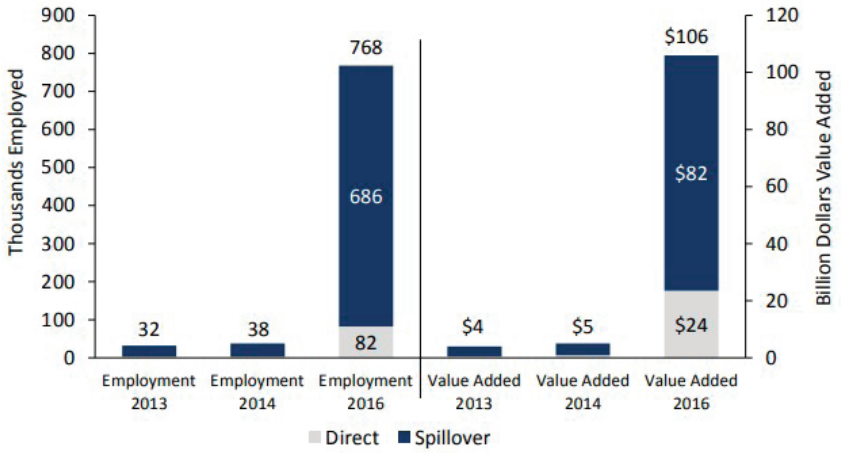


FIGURE ANNEX 3-1-3 Enzymes production: contribution to employment and value added, 2013, 2014, and 2016. NOTE: "Direct" is enzyme industry value added; "Spillover" accounts for interindustry linkages (indirect effects), as well as induced effects via linkages to final demand. SOURCE: Daystar et al., 2018, p. 43.

Annex 3-2
Identifying Intangible Assets

A widely used framework for studying intangible investment is summarized in Table Annex 3-2-1. Column 1 of the table lists the types of spending that are included as investments under this framework. This framework is used to study the productivity and growth impacts of innovation, typically in conjunction with the empirical neoclassical theory–based "growth-accounting" approach to measuring and studying the drivers of economic growth, including in macro-policy and international comparative settings.[44] In the United States, business intangible investment overtook business tangible investment in the 1990s, suggesting that intangibles have been a driver of U.S. economic growth since that time (see Figure Annex 3-2-1). By this metric, major economies in Asia (China, Japan) and most European economies are behind the U.S. economy.[45]

There are, of course, other frameworks for studying innovation and growth (e.g., endogenous growth theory and Schumpeterian growth theory).[46] These frameworks and the intangible capital approach rooted in neoclassical theory are, in fact, closely related and not mutually exclusive. Endogenous growth theory focuses on the impacts of scientific knowledge and suggests that the long-run growth rate of an economy reflects its propensity to invest in new ideas. Although the notion that taxes, research subsidies, researcher supply, and intellectual property (IP) rights can influence economic growth via their impacts on investments in R&D predates endogenous growth theory, the emergence of that theory firmly grounded these tools as supporting long-run macroeconomic growth. Schumpeterian approaches emphasize that innovation is associated with

[44]See, e.g., Corrado et al. (2013, 2018), OECD (2013), and Thum-Thysen et al. (2017) for the European Commission, and discussions in the 2006, 2007, and 2008 issues of the *Economic Report of the President of the United States*. Note that the framework is aligned with national accounts estimates consistent with the System of National Accounts 2008 (EC et al., 2009) to the extent that gross fixed capital formation includes computer software (which is believed to capture private databases); research and development (R&D); mineral exploration; and entertainment, artistic, and literary originals (i.e., the first five items listed in column 2 of Table Annex 3-2-1).

[45]The comparison is based on updated estimates of intangible investment in market sector industries for the European Union, Japan, and the United States as reported in Corrado et al. (2013) and OECD (2013); estimates for China cover all sectors of its economy (Hulten and Hao, 2012). For further information, see www.intaninvest.net.

[46]Endogenous growth theory stems from the contribution of Romer (1990); Schumpeterian theory was set out in a formal economic model by Aghion and Howitt (1992).

TABLE ANNEX 3-2-1 Categories and Types of Intangible Investment

Category	Types of Intangible Investment	Examples of Intangible Assets
Computerized information	• Software • Databases	• Digital capabilities, tools • Trade secrets, contracts
Innovative property	• Research and development • Mineral exploration • Entertainment, artistic, and literary originals • Other new product development (e.g., design originals, new financial products)	• Patents • Mineral rights • Licenses • Copyrights • Attributed designs • Trademarks
Economic competencies	• Employee training • Branding • Marketing research • Organizational structure/ business process investment	• Firm-specific human capital • Brand equity • Market insights, customer lists • Operating models, processes and systems

SOURCES: Corrado and Hulten, 2010, based on Corrado et al., 2005.

"creative destruction," in which the profit stream of a previous innovator is destroyed by the creation of a new innovator; this phenomenon suggests that policies aiming to balance IP protection against the profit-driven benefits of competition are warranted (and that there is much going on behind the macro-oriented approaches). The intangible framework tracks specific investments and mechanisms that drive commercial innovations based on breakthroughs in science (or other novelties), emphasizing the context-driven aspects of growth dividends to specific investments in specific industries.

With respect to valuing intangible assets, they are commonly regarded as company assets that are not physical.[47] Knowledge creation underlies the value of intangible assets (i.e., the types of spending listed in column 2 of Table Annex 3-2-1 produce knowledge of commercial [or public] value, examples of which are shown in column 3). As indicated in the main chapter text, replacement cost estimates are developed from time-series data on real investment using the "perpetual inventory method." That method cumulates real investments, period by period, after subtracting an estimate of economic depreciation during the period (the loss in the asset's value due to aging, holding time used in production constant).

[47]This is the view in financial accounting under U.S. Generally Accepted Accounting Principles; the definition there is simply "assets (not including financial assets) that lack physical substance."

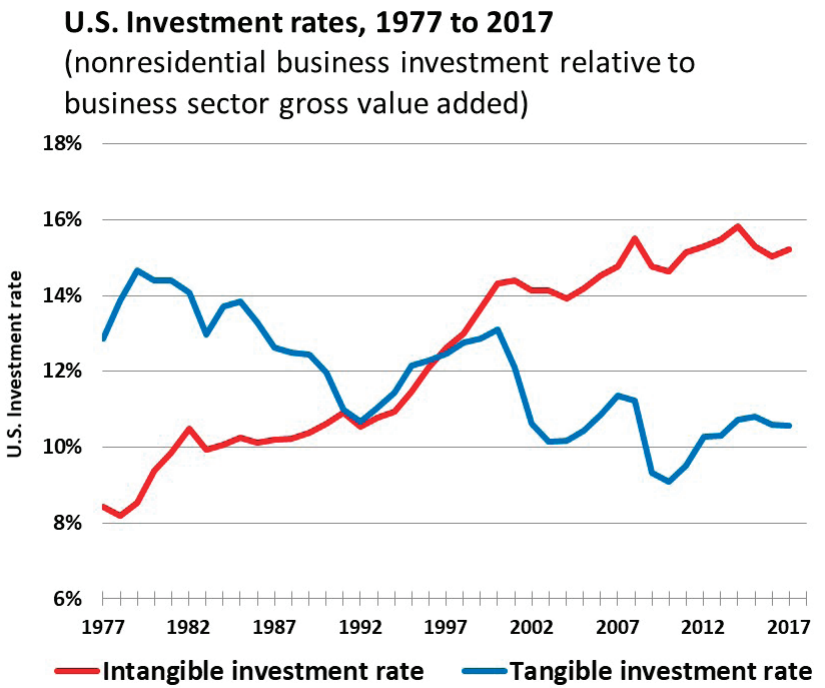


FIGURE ANNEX 3-2-1 U.S. investment rates, 1977–2017. SOURCE: Unpublished update to Corrado and Hulten (2010) at www.intaninvest.net.

This calculation produces an estimate of the volume of the stock; the value of the stock at replacement cost is obtained by multiplying the volume estimate by today's price.[48] Note that in companion wealth accounts, the national accounts' estimates of corporate assets at replacement cost are reconciled with the valuation of corporations in capital markets, connecting national accounting valuations to market valuations.[49] Some of the earliest studies of intangibles were motivated by the observation

[48]Note that a simple accumulation and correction for economic depreciation assumes that there are no natural disasters or noneconomic events that diminish the volume of net stocks; in practice, these "other changes in volume" are accounted for when such events (e.g., a hurricane) destroy capital. Note also that replacement cost differs from both the historical cost approach used in U.S. Generally Accepted Accounting Principles–consistent company financial accounts and the mark-to-market, or fair value, method that the International Financial Reporting Standards allows.

[49]"Companion wealth accounts" refers to the Integrated Macroeconomic Accounts (IMAs) produced jointly by the Bureau of Economic Analysis and the Federal Reserve Board. The IMAs present a sequence of accounts that relate income, saving, investment in real and financial assets, and asset revaluations to changes in wealth.

that firms' market valuations were systematically higher than both the value of the capital reported on corporate balance sheets and the tally of corporate assets at replacement cost in national accounts (e.g., Hall et al., 2001; Lev, 2001).

The replacement cost method for obtaining estimates of intangible assets depends on identifying consistent time series on investment in each asset and estimating a depreciation rate for the asset. Purchases of assets are relatively easy to track because a market transaction takes place; however, many intangible assets are developed within organizations. Estimates of this type of investment—called own-account investment—are based on the cost of the internal operation used to produce the asset. Regular surveys reveal the costs of the conduct of R&D within organizations. National accounts and the empirical literature on measuring intangibles (e.g., Corrado et al., 2009, 2013) exploit data on employee compensation by occupation (e.g., software engineers) to develop estimates of own-account investment in other intangible assets for industries or subsectors of the economy.[50]

Regarding depreciation rates, the notion that an asset's value will decline over time as a result of wear and tear or technological obsolescence is easy to understand, but estimating the rate at which this process takes place for a specific asset or class of assets is highly data demanding, and such estimates are few in number. Studies that consider estimation of depreciation for intangibles have shown that rates of depreciation for these assets vary by country, by industry, by firms within an industry, and over time.[51] And studies comparing rates of depreciation by asset type generally have found that R&D, design, and artistic assets are relatively long-lasting compared with software, organizational capital, and other economic competencies (training and brand).

In the context of a depreciation rate for an intangible asset, the idea is to capture the expected period of time for which the investment will yield returns. Based on a review of the literature and the conduct of new work (Li and Hall, 2019), the Bureau of Economic Analysis (BEA) concluded that it would hold the depreciation rate for business R&D for the national accounts fixed over time but allow it to vary by industry. On this basis, the rate of depreciation is estimated to be relatively rapid for R&D conducted by the computer equipment, computer system design, instruments, and software industries (22 to 40 percent per year). For pharmaceutical R&D, BEA uses a depreciation rate of 10 percent per year. For the scientific R&D industry (which includes a large share of biotech firms), BEA uses an R&D

[50]The wage costs are converted to estimates of total costs based on statistics for market production of similar activities/products.

[51]See the review and summary in Li and Hall (2018) (especially Table 1).

depreciation rate of 16 percent. A lower estimated rate of R&D depreciation in one industry compared with another is generally thought to be due to either a slower pace of technological change or a lesser degree of market competition (see Li and Hall [2019] for further discussion).

REFERENCES

AAAS (American Association for the Advancement of Science). 2019. Research by science and engineering discipline. https://www.aaas.org/programs/r-d-budget-and-policy/research-science-and-engineering-discipline (accessed December 20, 2019).

Aghion, P., and P. Howitt. 1992. A model of growth through creative destruction. *Econometrica* 60(2):323–351.

Ahmadpoor, M., and B. F. Jones. 2017. The dual frontier: Patented inventions and prior scientific advance. *Science* 357(6351):583–587.

Arboleda, H. 2001. *Satellite accounts for agribusiness*. Resource Paper Annex 5. Papers Presented at the Expert Consultation on Agricultural Statistics, 11–14 September. Bangkok, Thailand: UN FAO.

Arora, A., S. Belenzon, and A. Patacconi. 2019. The decline of science in corporate R&D. *Strategic Management Journal* 39(1):3–32.

Arrow, K. J., and G. Debreu. 1954. Existence of an equilibrium for a competitive economy. *Econometrica* 22(3):265–290.

Biasi, B., and P. Moser. 2018. *Effects of copyrights on science—evidence from the U.S. book republication program*. CEPR discussion papers 12651. doi: 10.3386/w24255.

Bresnahan, T. F., and M. Trajtenberg. 1995. General purpose technologies "Engines of growth"? *Journal of Econometrics* 65(1):83–108.

Brynjolfsson, E., D. Rock, and C. Syverson. 2018. *The productivity J-curve: How intangibles complement general purpose technologies*. NBER working paper w2518. https://www.nber.org/papers/w25148.pdf (accessed September 7, 2019).

Bush, V. 1945. *Science, the endless frontier: A report to the President by Vannevar Bush, Director of the Office of Scientific Research and Development*. Washington, DC: U.S. Government Printing Office.

Carlson, R. 2016. Estimating the biotech sector's contribution to the U.S. economy. *Nature Biotechnology* 34(3):247–255.

Carlson, R. 2019. Presentation to the National Academy of Sciences Panel on Safeguarding the Bioeconomy, Washington, DC, January 28, 2019. http://nas-sites.org/dels/studies/bioeconomy/meeting-1 (accessed October 30, 2019).

Close, K., C. Meier, and M. Ringel. 2015. *Making big data work: Biopharma*. Boston, MA: Boston Consulting Group. https://www.bcg.com/en-us/publications/2015/big-data-advanced-analytics-biopharmaceuticals-making-big-data-work-biopharma.aspx (accessed September 7, 2019).

Cockburn, I. M. 2006. Is the pharmaceutical industry in a productivity crisis? *Innovation Policy and the Economy* 7:1–32.

Corrado, C., and C. Hulten. 2010. How do you measure a "Technological Revolution"? *American Economic Review* 100(2):99–104.

Corrado, C., C. Hulten, and D. Sichel. 2005. Measuring capital and technology: An expanded framework. In *Measuring capital in the new economy*, Vol. 66, edited by C. Corrado, J. Haltiwanger, and D. Sichel. Chicago, IL: University of Chicago Press. Pp. 11–46. http://www.nber.org/chapters/c0202.pdf (accessed October 30, 2019).

Corrado, C., C. Hulten, and D. Sichel. 2009. Intangible capital and U.S. economic growth. *The Review of Income and Wealth* 55(3):661–685. https://doi.org/10.1111/j.1475-4991.2009.00343.x.

Corrado, C., J. Haskel, C. Jona-Lasinio, and M. Iommi. 2018. Intangible investment in the EU and US before and since the Great Recession and its contribution to productivity growth. *Journal of Infrastructure, Policy and Development* 2(1):205.

Corrado, C., J. Haskel, C. Joan-Lasinio, and M. Iommi. 2013. Innovation and intangible investment in Europe, Japan, and the United States. *Oxford Review of Economic Policy* 29(2):261–286.

Corrado, C., J. Haskel, and C. Jona-Lasinio. 2017. Public intangibles: The public sector and economic growth in the SNA. *Review of Income and Wealth* 63(Suppl 2):S355–S380.

Corrado, C., J. Haskel, C. Jona-Lasinio, and M. Iommi. 2018. Intangible investment in the EU and US before and since the Great Recession and its contribution to productivity growth. *Journal of Infrastructure, Policy and Development* 2(1):205.

Cumbers, J. 2019. *Defining the bioeconomy*. Presentation to the Committee on Safeguarding the Bioeconomy: Finding Strategies for Understanding, Evaluating, and Protecting the Bioeconomy While Sustaining Innovation and Growth. January 28, 2019. Washington, DC.

Daystar, J., R. B. Handfield, J. Golden, E. McConnell, and B. Morrison. 2018. *An economic impact analysis of the U.S. biobased products industry*. https://www.biopreferred.gov/BPResources/files/BiobasedProductsEconomicAnalysis2018.pdf (accessed September 7, 2019).

DiMasi, J. A., H. G. Grabowski, and R. W. Hansen. 2016. Innovation in the pharmaceutical industry: New estimates of R&D Costs. *Journal of Health Economics* 47:20–33. doi: 10.1016/j.jhealeco.2016.01.012.

EC (European Commission), International Monetary Fund, Organisation for Economic Co-operation and Development, United Nations, and World Bank. 2009. *System of national accounts 2008*. New York: United Nations.

Efken, J., W. Dirksmeyer, P. Kreins, and M. Mnecht, 2016. Measuring the importance of the bioeconomy in Germany: Concept and illustration. *NJAS—Wageningen Journal of Life Sciences* 77:9–17. https://doi.org/10.1016/j.njas.2016.03.008.

Ehrenfeld, W., and F. Kropfhäußer, 2017. Plant-based bioeconomy in Central Germany—a mapping of actors, industries and places. *Technology Analysis & Strategic Management* 29(5):514–527. doi: 10.1080/09537325.2016.1140135.

Feldman, M. P., D. F. Kogler, and D. L. Rigby. 2015. rKnowledge: The spatial diffusion and adoption of rDNA methods. *Regional Studies* 49(5):798–817.

Fernandez-Cornejo, J., S. Wechsler, and D. Milkove. 2016. *The adoption of genetically engineered alfalfa, canola, and sugarbeets in the United States*. Economic Information Bulletin EIB-163. Washington, DC: USDA ERS.

Furman, J. L., and S. Stern. 2011. Climbing atop the shoulders of giants: The impact of institutions on cumulative research. *American Economic Review* 101(5):1933–1963.

Furman, J., M. Nagler, and M. Watzinger. 2018. Disclosure and subsequent innovation: Evidence from the patent depository library program. NBER WP 24660. doi: 10.3386/w24660.

Gittelman, M. 2016. The revolution re-visited: Clinical and genetics research paradigms and the productivity paradox in drug discovery. *Research Policy* 45(8):1570–1585.

Golden, J. S., R. B. Handfield, J. Daystar, and T. E. McConnell. 2015. *An economic impact analysis of the US biobased products industry: A report to the Congress of the United States of America.* https://www.biopreferred.gov/BPResources/files/EconomicReport_6_12_2015.pdf (accessed September 7, 2019).

Graham, S. J., A. C. Marco, and R. Miller, 2018. The USPTO patent examination research dataset: A window on patent processing. *Journal of Economics & Management Strategy* 27(3):554–578.

Hall, B., A. Jaffe, and M. Trajtenberg. 2001. *The NBER patent citations data file: Lessons, insights and methodological tools.* National Bureau of Economic Research working paper #8498. Cambridge, MA: The MIT Press. doi: 10.3386/w8498.

Haskel, J., and S. Westlake. 2017. *Capitalism without capital: The rise of the intangible economy.* Princeton, NJ: Princeton University Press.

Henderson, R., and I. Cockburn. 1996. Scale, scope, and spillovers: Determinants of research productivity in the pharmaceutical industry. *RAND Journal of Economics* 27(1):32–59.

Hermans, R., A. Loffler, and S. Stern. 2007. *The globalization of biotechnology: Science-driven clusters in a flat world.* Washington, DC: The National Academies STEP Board and Northwestern University.

Holloway, T. M., and J. S. Reeb. 1989. A price index for biomedical research and development. *Public Health Reports* 104(1):11–13.

Hulten, C. R., and J. X. Hao. 2012. The role of intangible capital in the transformation and growth of the Chinese economy. *National Bureau of Economic Research*. Working Paper 18405.

Jaffe, A. B., and J. Lerner. 2004. *Innovation and its discontents: How our broken patent system is endangering innovation and progress, and what to do about it.* Princeton, NJ: Princeton University Press.

Jones, R., and J. R. Wilsdon. 2018. *The biomedical bubble: Why U.K. research and innovation needs a greater diversity of priorities, politics, places and people*. London, UK: NESTA.

Kogan, L., D. Papanikolaou, A. Seru, and N. Stoffman. 2017. Technological innovation, resource allocation, and growth. *Quarterly Journal of Economics* 132(2):665–712.

Lev, B. 2001. *Intangibles: Management, measurement and reporting*. Washington, DC: Brookings Institution Press.

Lev, B., and F. Gu. 2016. *The end of accounting and the path forward for investors and managers.* Wiley Finance Series. Hoboken, NJ: John Wiley & Sons.

Levin, R. C., A. K. Klevorick, R. R. Nelson, S. G. Winter, R. Gilbert, and Z. Griliches. 1987. Appropriating the returns from industrial research and development. *Brookings Papers on Economic Activity* 3:783–831.

Li, W. C. Y., M. Nirei, and K. Yamana. 2019. *Value of data: There's no such thing as a free lunch in the digital economy*. RIETI discussion paper 19-E-022. https://www.bea.gov/research/papers/2018/value-data-theres-no-such-thing-free-lunch-digital-economy (accessed October 30, 2019).

Lier, M., M. Aarne, L. Kärkkäinen, K. T. Korhonen, A. Yli-Viikari, and T. Packalen. 2018. *Synthesis on bioeconomy monitoring systems in the EU member states: Indicators for monitoring the progress of bioeconomy*. https://jukuri.luke.fi/handle/10024/542249 (accessed August 30, 2019).

Machlup, F. 1961. Patents and inventive effort. *Science* 133(3463):1463–1466.

Mansfield, E. 1986. Patents and innovation: An empirical study. *Management Science* 32:173–181.

Marco, A. C., and R. D. Miller. 2019. Patent examination quality and litigation: Is there a link? *International Journal of the Economics of Business* 26(1):65–91.

Miller, R. E., and P. D. Blair. 2009. *Input-output analysis: Foundations and extensions*, 2nd edition. Cambridge, UK: Cambridge University Press.

Nagaraj, A. 2018. *The private impact of public information: Landsat satellite maps and gold exploration*. http://abhishekn.com/files/nagaraj_landsat_oct2018.pdf (accessed October 30, 2019).

NASEM (National Academies of Sciences, Engineering, and Medicine). 2017. *Preparing for future products of biotechnology.* Washington, DC: The National Academies Press. https://doi.org/10.17226/24605.

NASEM. 2018. *Biodefense in the age of synthetic biology*. Washington, DC: The National Academies Press. https://doi.org/10.17226/24890.

NASEM. 2019. *Improving data collection and measurement of complex farms*. Washington, DC: The National Academies Press. https://doi.org/10.17226/25260.

NRC (National Research Council). 2009. *Intangible assets: Measuring and enhancing their contribution to corporate value and economic growth: Summary of a workshop*. Washington, DC: The National Academies Press. https://doi.org/10.17226/12745.

NSB and NSF (National Science Board and National Science Foundation). 2018. *2018 Science & Engineering Indicators*. https://www.nsf.gov/statistics/2018/nsb20181/assets/nsb20181.pdf (accessed September 11, 2019).

OECD (Organisation for Economic Co-operation and Development). 2013. *Supporting investment in knowledge capital, growth and innovation*. Paris, France: OECD Publishing. https://doi:.org/10.1787/9789264193307-en.

OECD/Eurostat. 2018. *Oslo Manual 2018: Guidelines for collecting, reporting and using data on innovation,* 4th edition. Paris, France: OECD Publishing. doi: 10.1787/9789264304604-en.

Otto, R., A. Santagostino, and U. Schrader. 2014. *Rapid growth in biopharma: Challenges and opportunities*. New York: McKinsey & Company.

Pakes, A., and Z. Griliches. 1980. Patents and R&D at the firm level: A first report. *Economics Letters* 5:377–381.

Pammolli, F., L. Magazzini, and M. Riccaboni. 2011. The productivity crisis in pharmaceutical R&D. *Nature Reviews Drug Discovery* 10:428–438. doi: 10.1038/nrd3405.

Philp, J., and D. Winickoff. 2018. *Realising the circular bioeconomy*. Paris, France: OECD Publishing. http://www.wcbef.com/assets/Uploads/Publications/Realising-the-Circular-Bioeconomy.pdf (accessed August 30, 2019).

Popkin, J., and K. Kobe. 2010. *Manufacturing resurgence: A must have for U.S. prosperity.* https://www.nist.gov/sites/default/files/documents/2017/04/28/id61990_ManufacturingResurgence.pdf (accessed September 7, 2019).

Rock, D. 2018. *Engineering value: The returns to technological talent and investments in artificial intelligence.* https://www.gsb.stanford.edu/sites/gsb/files/jmp_daniel-rock.pdf (accessed September 7, 2019).

Romer, P. 1990. Endogenous technological change. *Journal of Political Economy* 98(5):S71–S102.

Scannell, J. W., A. Blanckley, H. Boldon, and B. Warrington. 2012. Diagnosing the decline in pharmaceutical R&D efficiency. *Nature Reviews Drug Discovery* 11:1–10.

Scherer, F. M. 1983. The propensity to patent. *International Journal of Industrial Organization* 1:107–128.

Stokes, D. E. 1997. *Pasteur's quadrant: Basic science and technological innovation*. Washington, DC: Brookings Institution Press.

Thum-Thysen, A., P. Voigt, B. Bilbao-Osorio, C. Maier, and D. Ognyanova. 2017. *Unlocking investment in intangible assets*. Brussels, Belgium: Publication Office of the European Union.

USDA ERS (U.S. Department of Agriculture Economic Research Service). n.d. *Adoption of genetically engineered crops in the U.S. data product.* https://www.ers.usda.gov/data-products/adoption-of-genetically-engineered-crops-in-the-us (accessed October 21, 2019).

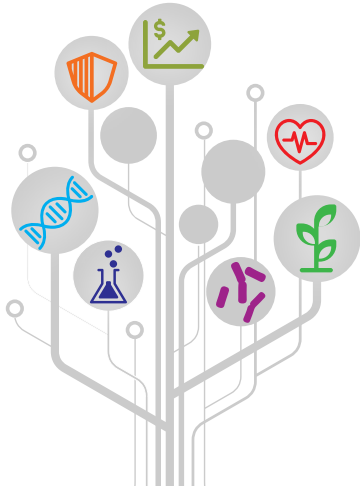
USDA NASS (U.S. Department of Agriculture National Agricultural Statistical Service). *2017 Census of Agriculture. United States summary and state data*, Volume 1. Geographic Area Series, Part 51, AC-17-A-51. Washington, DC: USDA.

USGCRP (U.S. Global Change Research Program). 2018. *Impacts, risks, and adaptation in the United States: Fourth national climate assessment, Volume II: Report-in-brief*, edited by D. R. Reidmiller, C. W. Avery, D. R. Easterling, K. E. Kunkel, K. L. M. Lewis, T. K. Maycock, and B. C. Stewart. Washington, DC: USGCRP. https://nca2018.globalchange.gov/downloads (accessed September 7, 2019).

Varian, H. 2018. *Artificial intelligence, economics, and industrial organization*. Working Paper #24839. https://www.nber.org/papers/w24839.pdf (accessed November 9, 2019).

Wesseler, J., and J. von Braun. 2017. Measuring the bioeconomy: Economics and policies. *Annual Review of Resource Economics* 9:275–298.

Wilson Center. 2013. *Tracking the growth of synthetic biology: Findings for 2013*. https://www.cbd.int/doc/emerging-issues/emergingissues-2013-07-WilsonCenter-Synbio_Maps_Findings-en.pdf (accessed September 7, 2019).



4 AREAS OF LEADERSHIP IN THE GLOBAL ECONOMY

Summary of Key Findings

- Internationally, the United States is the leader in the commercialization of advances in synthetic biology and continues to hold an advantage in terms of the education of new Ph.D.s in the life sciences. This position provides the basis for but no guarantee of future leadership in bioeconomy innovation.

This chapter identifies metrics commonly used to determine strategic leadership positions in the global economy and provides an overview of those areas of the bioeconomy in which the United States currently maintains a leadership position. In particular, U.S. investments and outputs in science, innovation, and entrepreneurship are compared with those of other countries investing heavily in the bioeconomy. Although the United States has maintained leadership in many domains of science and innovation since World War II, the set of leading innovator nations has expanded substantially over the past few decades with continued growth in investments in education and innovative capacity on the part of such

countries as Germany, Israel, Singapore, South Korea, and, increasingly, China (Furman and Hayes, 2004; Furman et al., 2002).

Concerns about the future leadership of the United States in key segments of science and innovation have been raised in numerous forums (see, e.g., American Academy of Arts & Sciences, 2014; McNutt, 2019; NAS et al., 2010; NRC, 2007). Many of the foundational scientific and technical advances that enable the bioeconomy were pioneered in the United States. These advances include Herbert Boyer and Stanley Cohen's invention of recombinant-DNA technology in 1973, which arguably launched the biotechnology industry. They also include subsequent advances in genome editing enabled by clustered regularly interspaced short palindromic repeats (CRISPR)/Cas-9 technology, initially demonstrated for potential use as a tool by Jennifer Doudna and Emmanuelle Charpentier in 2012 (Doudna and Charpentier, 2014; Jinek et al., 2012) and further developed by a number of research teams (Cho et al., 2013; Cong et al., 2013; Mali et al., 2013; Slaymaker et al., 2016; Suzuki et al., 2016; Qi et al., 2013). Leadership in initial scientific discovery does not, however, guarantee subsequent leadership in science or innovation. This observation is dramatically illustrated by the case of Great Britain's early leadership in the chemistry of aniline dyes, the impetus having been provided by the early discoveries of William Henry Perkin in the mid-1850s. Britain's leadership was subsequently eclipsed by the industrial scientific and technological leadership of the German chemical and dye industries in the 1860s and German leadership in biology, pharmaceuticals, and medicine in the subsequent decades of the 1870s and 1880s (Murmann, 2003).

LEADERSHIP IN SCIENCE IN THE BIOECONOMY

Paul Krugman (1991) famously stated that knowledge flows are exceptionally difficult to measure because, unlike physical goods, they do not leave a clear trace. This fundamental measurement problem has frustrated the study of knowledge creation, knowledge spillovers, and innovation despite the best efforts of researchers and policy makers. The measurement problems are even greater in the context of international studies of knowledge creation, leadership, and competitiveness, as such advances have different meanings in different contexts. For example, shop floor workers may achieve new-to-the-world innovations in manufacturing in mechanized factories with no immediate relevance to factories that rely on manual labor, whereas new-to-the-world innovations may be achieved in countries that rely on manual labor for manufacturing that may be of limited or no relevance in locations characterized by a high degree of factory automation. Adding to the difficulty of measuring knowledge creation across nations is the problem that countries, particularly those

not at the frontier of knowledge generation, have typically underinvested in the collection of data.

The measurement problem is particularly acute in the context of industry sectors, such as the bioeconomy, whose definition varies across countries and whose output is not measured in a systematic way, even within most individual countries. The following outline of the metrics for identifying strategic leadership positions in the global bioeconomy thus relies on a range of measures.

Comparisons of Government Research and Development Expenditures on the Bioeconomy

One valuable measure of scientific leadership in the bioeconomy would involve comparing time-series data on total government expenditures on research and development (R&D) in the bioeconomy. These data would ideally be converted into real rather than nominal dollars to capture the impact of inflation and would include measures of both the flows of expenditures (i.e., annual expenditures in each year) and the stock of expenditures (i.e., accumulated expenditures, adjusted to reflect the depreciation of knowledge over time). The committee was unable to find a historical data series of government expenditures on biotechnology or other aspects of the bioeconomy from either the National Science Foundation (NSF) or the Organisation for Economic Co-operation and Development (OECD) that compares the United States with a wide range of other countries. OECD does report a data series for a set of countries not including the United States (see Figure 4-1). This series compares intramural biotechnology R&D expenditures in the government and higher-education sectors as a fraction of total government and higher-education sector R&D expenditures. It is difficult to compare these data effectively across nations, however, because of differences in the mode of data collection. Nonetheless, one point that does appear clear is that relative to historical investment, South Korea, and, to some degree, Spain and the Czech Republic, have begun to accelerate investments in biotechnology. The data suggest that South Korea devoted nearly $3.4 billion to government and higher-education spending on biotechnology in 2016. A related though not directly comparable figure for the United States is that in fiscal year 2015, agencies of the U.S. federal government, principally the Department of Health and Human Services, obligated $30.5 billion to the life sciences (see Figure 4-2). Of this amount, $14.8 billion was targeted to general biological sciences, $10.9 billion to medical sciences, $1.3 billion to agricultural sciences, $0.8 billion to environmental sciences, and $2.6 billion to other life sciences (NSB and NSF, 2018, Appendix Table 4-25). While not all of the bioeconomy is based on life sciences, these

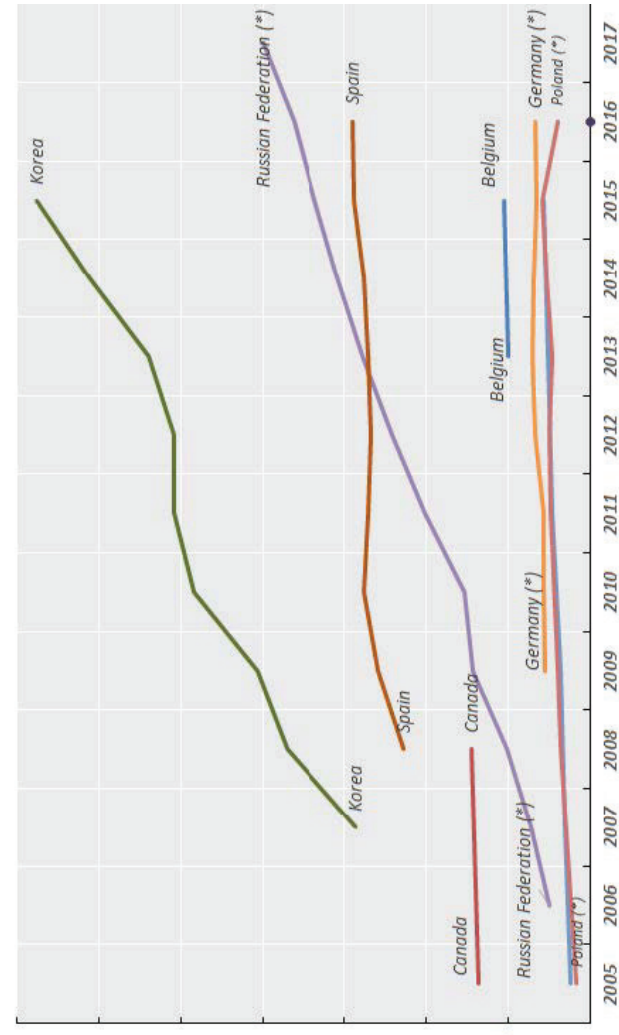


FIGURE 4-1 Intramural biotechnology R&D expenditures in the government and higher-education sectors, selected Organisation for Economic Co-operation and Development (OECD) countries, 2005–2016 ($US millions Purchasing Power Parity). NOTES: For Germany, total public federal bioeconomy R&D expenditures exclude the higher-education sector. For Poland, they include the private nonprofit sector. For the Russian Federation, a proxy indicator is used: R&D expenditure in life sciences (before 2011, "living systems"), which includes bioengineering, biocatalysis, biosynthesis and biosensor technologies, biomedical and veterinary technologies, genomics and pharmacogenetics, and living cell technologies. SOURCE: OECD, Key Biotechnology Indicators, http://oe.cd/kbi, updated October 2018.

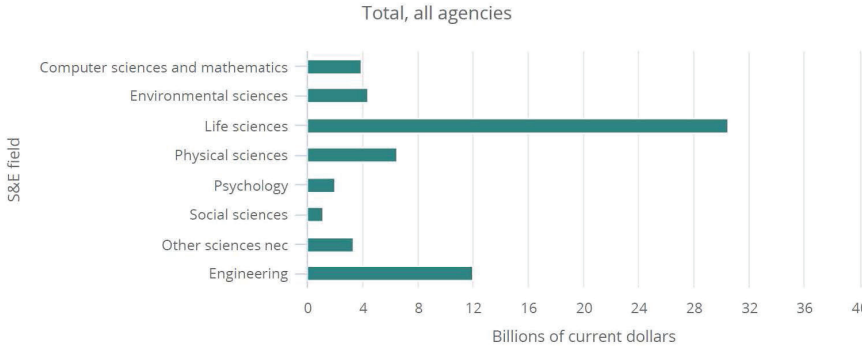


FIGURE 4-2 Federal obligations for research, across all agencies and by major science and engineering field, fiscal year 2015. SOURCE: NSB and NSF, 2018, Figure 4-12.

data suggest that the United States remains among the world's leaders in government-led investment in the biological sciences.

Comparisons of Scientific Output in the Bioeconomy

A second, valuable indicator of scientific leadership in the bioeconomy can be gleaned from measures of scientific output, that is, academic publications. Numerous sources, including Thompson Reuters Web of Knowledge, Elsevier's Scopus database, and Microsoft Academic, provide primary information on numbers of academic publications. Categorizing publications according to scientific fields is a challenge, but data agencies, including OECD and NSF, compile indicators using these primary data. Individual researchers can do the same.

Figure 4-3 reports counts of science and engineering publications in Scopus, by selected region and field, for 2016, based on an analysis performed by NSF for the *Science and Engineering Indicators* (S&E).[1] These data show that the United States leads the world in the production of publications in the biological and medical sciences (although the collec-

[1]The use of academic publications and citations as indicators of scientific output and leadership has become the subject of a large body of research, including studies in the field of scientometrics (de Solla Price, 1976; Garfield, 1979; Leydesdorff, 2001; Schoenbach and Garfield, 1956). Research has noted the limitations of this approach, including the potential for strategic and reputation-based citation (Simkin and Roychowdhury, 2003). Nonetheless, country-level counts of publications have proven useful in understanding broad trends in scientific progress and as a result, are regularly included among the statistics gathered and reported by NSF's S&E.

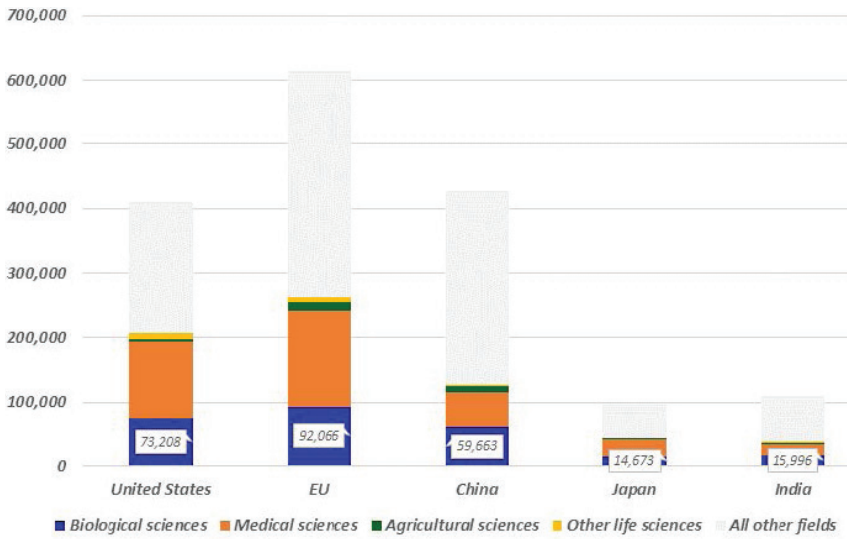


FIGURE 4-3 Counts of science and engineering publications in Scopus, by selected region and field, 2016. NOTES: EU = European Union. Data callouts indicate the number of publications in the biological sciences. Article counts are from a selection of journals in science and engineering from Scopus. Articles are classified by their year of publication and are assigned to a region, country, or economy on the basis of the institutional address(es) listed in the article. Articles are credited on a fractional-count basis in which, for example, if two authors of different nationalities co-wrote a paper, each of their countries would be credited with one-half of a paper. See Appendix Table 5-26 in *Science and Engineering Indicators* (S&E) *2018* for regions, countries, and economies included in the EU. Percentages may not add to 100 percent because of rounding. SOURCE: National Science Foundation, National Center for Science and Engineering Statistics, S&E 2018 (Table 5-23), based on SRI International; Science-Metrix; Elsevier, Scopus abstract and citation database (accessed July 2017).

tive publication output of the countries of the European Union exceeds that of the United States). The output of publications in the biological and medical sciences with author addresses based in China is, however, quite striking, particularly compared with historical levels. The rise of Chinese biotechnology is documented in Figure 4-4, which reports annual biotechnology publications in the United States and China based on an analysis by Gryphon Scientific & Rhodium Group in its 2019 report *China's Biotechnology Development*. The data shown in Figure 4-4 document a substantial rise in biotechnology research output over the past decade, with acceleration beginning around 2011 across a number of regions. While the biotechnology publication output for both the European Union and China

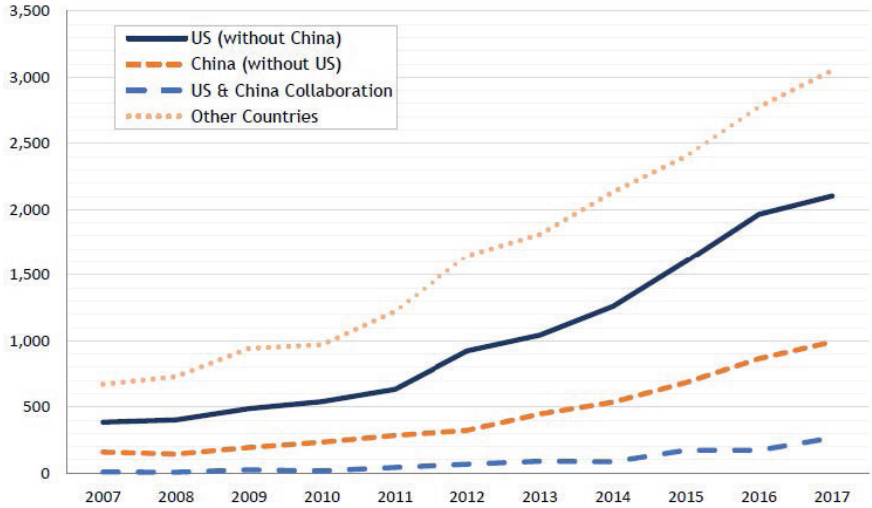


FIGURE 4-4 Annual biotechnology publications, United States versus China, 2000–2017. SOURCE: Computed by Gryphon Scientific and Rhodium Group (2019, Figure 1-2) based on Scopus data, using English-language publication search on keywords, "CAR-T" OR ("therapeutic antibodies") OR (CRISPR AND editing OR engineering) OR (synthetic biology) OR "metabolic engineering" OR (genomics AND "precision medicine" OR "personalized medicine") OR agrobacterium OR (CRISPR AND plants).

has risen substantially, these data do not suggest that either region is on a trajectory to eclipse the output of the United States in the short term.

Comparisons of Scientific Training for the Bioeconomy

A third important measure that can be used to compare global bioeconomy leadership is the training of scientific and technical personnel. As is true for both government investment and scientific output, there are limitations to the data on the bioeconomy workforce. In particular, it is easier to measure the output of recently trained graduates in particular scientific disciplines than to track the total count of employees in the bioeconomy workforce. This is due, in part, to the complexities of measuring the bioeconomy workforce. Whereas it is relatively straightforward to classify individuals with Ph.D.s in biology as potential contributors to the bioeconomy, it is more difficult to count the number of individuals trained in areas that are complementary contributors to the bioeconomy, including, for example, those with specific training in data analytics, computer

science, automation, the marketing of biologic medicines, or logistics for the transportation of biofuels.[2]

Cross-country comparisons of the count of doctoral graduates by field are available from OECD for 2016. Figure 4-5 reports these data for students identified as having completed degrees in "biological and related sciences." In concordance with the publication and investment measures reported above, these data provide evidence of U.S. bioeconomy leadership. The United States awarded more than twice as many doctorates in 2016 as Germany, the next most prolific country for which data are available. Note, however, that OECD is not able to report either the total number of doctorates awarded in China or the number granted in biological and related sciences. Note as well that OECD data represent both imprecise estimates and underestimates of the total number of doctorate recipients in fields related to the bioeconomy. For example, NSF reports for 2016 that the United States produced 12,568 doctorate recipients in life sciences (which includes (1) agricultural and natural sciences, (2) biological and biomedical sciences, and (3) health sciences), plus another 1,089 doctorate recipients in bioengineering and biomedical engineering.[3]

Data that track over time the number of recipients of doctoral degrees

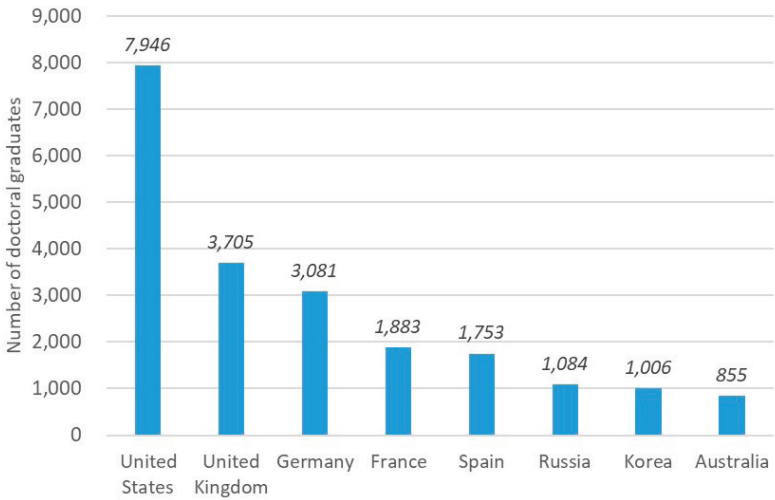


FIGURE 4-5 Doctoral graduates in biological and related sciences, 2016. SOURCE: The committee's calculations based on data extracted from https://stats.oecd.org (accessed July 2019).

[2]It is important to note that counts of doctorate recipients may not be fully consistent across countries, as countries do vary in their expectations for doctoral student work.

[3]See https://www.nsf.gov/statistics/2018/nsf18304/data/tab12.pdf.

in the biosciences by country of citizenship are not publicly available in a curated dataset. The closest estimates come from the S&E, which collates data from various country sources on the number of degrees awarded in a country by broad academic field. Figure 4-6 shows an increase in the number of doctoral degrees in the combined category of physical and biological sciences, mathematics, and statistics for selected countries in the years 2000, 2007, and 2014. These data exclude some degrees that apply to the bioeconomy, such as bioengineering, yet because the data include degrees in mathematics, statistics, and physical sciences, they likely include doctoral students beyond those trained for specific work in the bioeconomy. These limitations notwithstanding, the key features of the data are that the United States leads in the number of doctoral degrees in fields pertinent

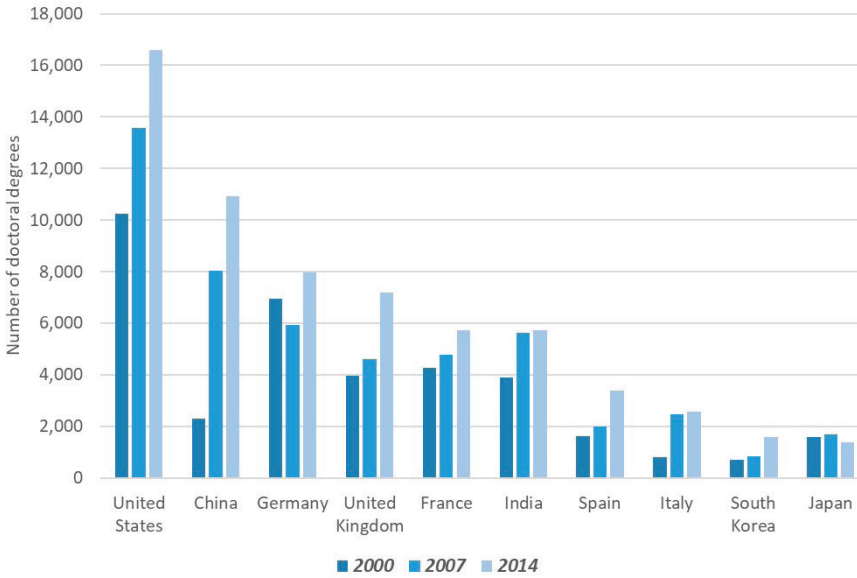


FIGURE 4-6 Number of doctoral degrees in physical and biological sciences, mathematics, and statistics, selected countries and selected years, 2000–2014. NOTES: Data for China exclude computer sciences, as these are counted under engineering rather than physical and biological sciences, mathematics, and statistics. Data for Japan include thesis doctorates, called *ronbun hakase*, earned by employees in industry. In data on higher education for Japan, mathematics is included in natural sciences (included on this chart), and computer sciences are included in engineering (not included). Data for doctoral degrees use International Standard Classification of Education level 8. Science degree data do not include health fields. Data for India are for 2006 rather than 2007. SOURCE: Compiled based on NSB and NSF, 2018 (Appendixes 2-38 and 2-39).

to the bioeconomy granted throughout the period (though the number of degrees from China saw the greatest growth over the period). If the current rates of growth persist, China will soon surpass the United States in the awarding of such degrees.

Given that doctoral trainees are the engine powering the advances in basic research at academic institutions, being able to supplement the United States' bioeconomy workforce with talented students from around the world is a benefit. Among the roughly 45,000 recipients of doctoral degrees within the United States, about 30–34 percent are students on temporary visas, the largest fraction of whom are of Chinese origin. Table 4-1 reports a number of key facts about Ph.D. graduates of U.S. institutions between 2011 and 2017 who did not hold U.S. citizenship. Several facts are notable. First, citizens from China, India, and South Korea constitute the largest number of non-U.S. citizens who completed doctoral degrees at U.S. academic institutions in 2011 and 2017. Furthermore, among Asian countries, China experienced the greatest increase in the number of citizens completing U.S.-based doctorates, a boost of approximately 40 percent in 2017 relative to the nearly 4,000 Chinese citizen students who completed their degree in 2011. Interestingly, however, the fraction of doctoral students staying in the United States remained relatively constant across countries, including China, during the period 2011–2017.

For selected countries, S&E reports the total number of doctoral degrees awarded by U.S. institutions, by scientific field and citizenship of recipient, for the period 1995–2015. Data for China, India, South Korea, and Taiwan are presented in Table 4-2. Nearly 70,000 students with Chinese citizenship received doctoral degrees in science and engineering fields from U.S. institutions during this time. Of these individuals, 12,002 earned degrees in biological sciences, and 10,816 earned degrees in physical sciences.

Taken together, these indicators suggest that the United States continues to lead the world in government investments and outputs as well as the production of doctorate recipients in sciences related to the bioeconomy. This leadership does not, however, appear to be as secure as it once was. China, in particular, has begun to increase its investments at a rapid rate and appears poised to overtake the United States at least in the production of doctoral recipients in these bioeconomy-related sciences in the medium term (see Gryphon Scientific and Rhodium Group, 2019).

NATIONAL COMPARISONS OF PRIVATE INNOVATION INPUTS

Whereas the prior chapter highlighted government expenditures on R&D investments relevant to the bioeconomy, this section of this chapter

TABLE 4-1 Doctorate Recipients with Temporary Visas, by Year of Degree and Intent to Stay in the United States After Receiving Degree (All Degrees), by Country of Citizenship, 2011–2017

Country of Citizenship	2011		2017		Total, All Years, 2011–2017		Percent Change, 2011–2017	
	Number	% Staying	Number	% Staying	Number	% Staying	Number	% Staying
All temp. visa holders	14,235	70.1	16,323	74.2	109,476	71.5	15	6
Americas	1,449	57.3	1,443	56.6	10,370	56.4	0	–1
Asia	9,568	74.5	10,659	80.0	73,431	76.4	11	7
China	3,988	82.1	5,564	83.2	34,458	81.9	40	1
India	2,165	84.6	1,974	88.6	15,335	85.8	–9	5
South Korea	1,445	60.0	1,126	68.5	9,173	62.4	–22	14
Europe	1,962	64.3	1,788	67.4	12,994	63.8	–9	5
France	125	64.8	107	69.2	790	63.7	–14	7
Germany	203	65.5	154	68.2	1,340	58.1	–24	4
Italy	137	60.6	161	70.8	1,069	64.8	18	17
Turkey	493	61.9	498	61.0	3,275	61.0	1	–1
Middle East	600	61.3	1,509	62.1	7,052	64.4	152	1
Iran	198	88.9	771	92.6	3,472	90.1	289	4
Saudi Arabia	49	14.3	340	10.3	996	11.9	594	–28

NOTE: Percentages based on all doctorate recipients on temporary visas who indicated where they intended to stay after graduation (United States versus foreign location), not just those with definite commitments for employment or postdoctoral study.
SOURCE: National Science Foundation, National Center for Science and Engineering Statistics, 2018 Survey of Earned Doctorates.

TABLE 4-2 Asian Recipients of U.S. Science and Engineering Doctorates on Temporary Visas, by Field and Country or Economy of Origin, 1995–2015

Field	Asia	China	India	South Korea	Taiwan
All fields	166,920	68,379	32,737	26,630	16,619
Science and engineering	146,258	63,576	30,251	20,626	13,001
Engineering	55,215	23,101	13,208	8,274	5,045
Science	91,043	40,475	17,043	12,352	7,956
Agricultural sciences	4,927	1,745	823	720	441
Biological sciences	25,149	12,202	5,654	2,459	2,374
Computer sciences	9,287	4,229	2,477	1,015	597
Earth, atmospheric, and ocean sciences	2,803	1,563	357	338	228
Mathematics	7,494	4,493	805	967	503
Medical and other health sciences	5,298	1,368	1,371	672	878
Physical sciences	20,528	10,816	3,516	2,216	1,305
Psychology	2,053	530	277	481	320
Social sciences	13,504	3,529	1,763	3,484	1,310
Non–science and engineering	20,662	4,803	2,486	6,004	3,618

NOTES: Asia includes Afghanistan, Bangladesh, Bhutan, Brunei, Burma, Cambodia, China, Christmas Island, Hong Kong, India, Indonesia, Japan, Kazakhstan, Kyrgyzstan, Laos, Macau, Malaysia, Maldives, Mongolia, Nepal, North Korea, Pakistan, Papua New Guinea, Paracel Islands, Philippines, Singapore, South Korea, Spratly Islands, Sri Lanka, Taiwan, Tajikistan, Thailand, Timor-Leste, Turkmenistan, Uzbekistan, and Vietnam. Data include temporary visa holders and non-U.S. citizens with unknown visa status who are assumed to be on temporary status.
SOURCE: *Science and Engineering Indicators 2018*, National Science Foundation, National Center for Science and Engineering Statistics, 2015 Survey of Earned Doctorates.

transitions to focus on overall national investments and investments from the private sector. These data tell a story similar to that in prior sections of this chapter. While the United States maintains leadership in bioeconomy investments, questions arise about the nation's ability to maintain its historical leadership position across science and engineering sectors.

Figures 4-7 and 4-8, respectively, report total national expenditures on R&D and the percentage of gross domestic product (GDP) devoted to R&D for countries allocating the most resources to R&D for the year 2015. Figure 4-7 shows that the United States continues to lead the world in total investment in innovation, with nearly $500 billion invested in R&D in 2015. China, however, is now investing an amount that is increasingly close to that of the United States, with more than $400 billion having been invested in 2015. Both countries invest more than the total invested by the European Union, which was $386.5 billion in that same year. Indeed, no country other than China invests even half as much in innovation as does the United States. It is not the case, however, that the United States leads the world in investment relative to the size of its economy. Figure 4-8 shows that numerous countries, including Austria, Denmark, Finland,

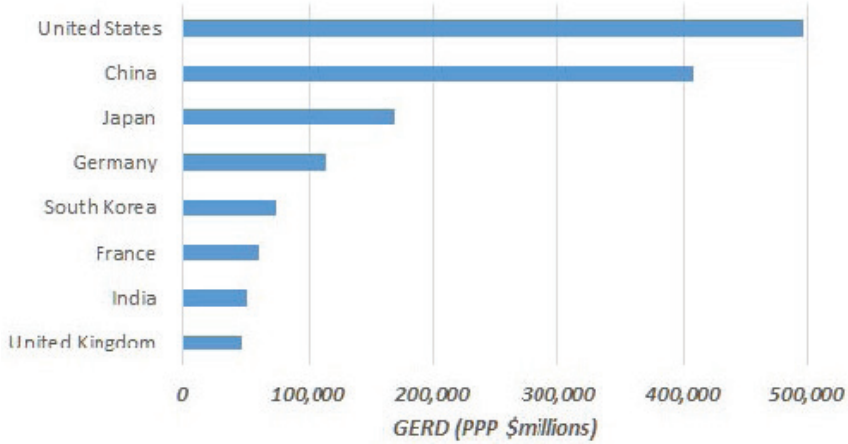


FIGURE 4-7 Purchasing power parity (PPP)-adjusted gross domestic expenditures on R&D (GERD), selected countries, 2015. NOTE: Data shown here reflect international standards for calculating GERD, which vary slightly from the National Science Foundation's methodology for tallying total U.S. R&D. SOURCES: National Science Foundation, *Science and Engineering Indicators 2018*, based on National Center for Science and Engineering Statistics, National Patterns of R&D Resources (annual series); OECD, Main Science and Technology Indicators (2017/1); United Nations Educational, Scientific and Cultural Organization Institute for Statistics Data Centre, http://data.uis.unesco.org (accessed October 13, 2017).

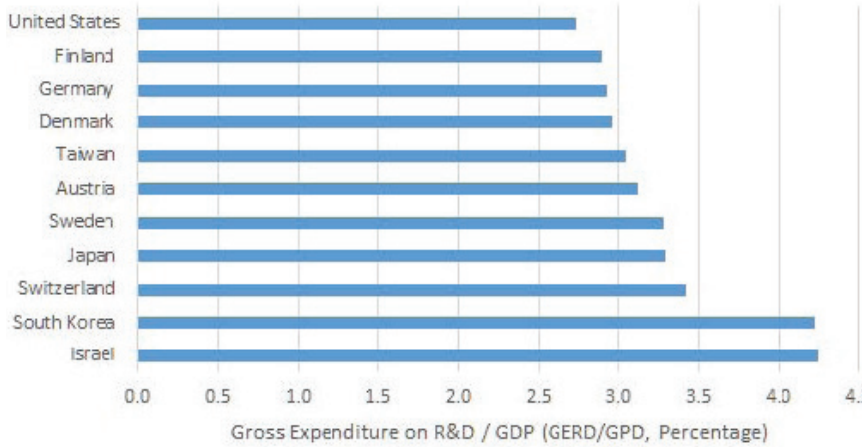


FIGURE 4-8 Percentage of gross domestic product devoted to gross expenditure on R&D (GERD/GDP %), selected countries, 2015. NOTE: Data shown here reflect international standards for calculating GERD, which vary slightly from the National Science Foundation's methodology for tallying U.S. total R&D. SOURCES: National Science Foundation, *Science and Engineering Indicators 2018*, based on National Center for Science and Engineering Statistics, National Patterns of R&D Resources (annual series); OECD, Main Science and Technology Indicators (2017/1); United Nations Educational, Scientific and Cultural Organization Institute for Statistics Data Centre, http://data.uis.unesco.org (accessed October 13, 2017).

Germany, Israel, Japan, South Korea, Sweden, Switzerland, and Taiwan, invest a higher fraction of GDP in R&D relative to the United States, while Figure 4-9 demonstrates that U.S. R&D investment as a share of GPD has remained stable even as that of other countries, such as South Korea and Japan, has continued to rise.

NATIONAL COMPARISONS OF INNOVATION IN BIOTECHNOLOGY AND OTHER AREAS OF THE BIOECONOMY

Ideal data on country-level investment in the bioeconomy are difficult to obtain. Indeed, it is difficult to obtain reliable data on R&D investment for even the largest bioeconomy segments, including one of the oldest, biotechnology. OECD compiles data on the number of firms active in biotechnology (see Figure 4-10). The presented data do not include China, for which information on aggregate R&D investment in biotechnology does not appear to be available in a reliable way (see Gryphon Scientific and Rhodium Group, 2019, pp. 13 and 36). The data in Figure 4-10 suggest, however, that the United States contains the largest number of biotechnology

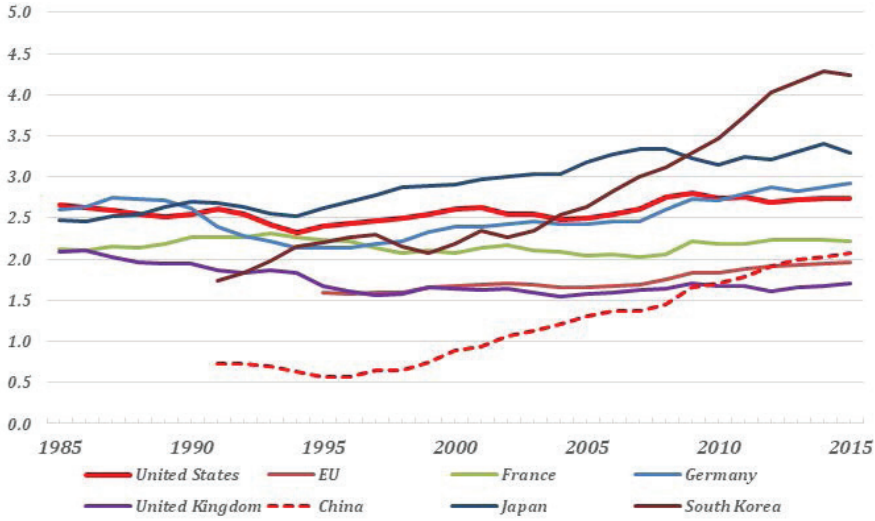


FIGURE 4-9 Gross domestic expenditures on R&D as a share of gross domestic product by the United States, the European Union (EU), China, and selected other countries, 1985–2015. SOURCE: NSB and NSF, 2018.

firms of any country in the world—more than 3,000 in 2015. Furthermore, U.S. private-sector firms invest an order of magnitude more heavily in biotechnology relative to firms in other countries. According to OECD, U.S. firms invested approximately $40 billion in biotechnology R&D in 2015, an amount that exceeded the combined investments of other leading countries in biotechnology (i.e., Belgium, Denmark, France, Germany, South Korea, and Switzerland) (see Figure 4-11). The United States is also a clear leader in OECD's counts of firms active in biotechnology R&D (see Figure 4-10), although these data are particularly difficult to compare across countries.

Data on international patenting suggest that U.S. leadership in biotechnology R&D remains substantial (see Figure 4-12). OECD compiles data on the fraction of biotechnology patents originating from inventors in each country, counting patents based on the fraction of inventors that come from that country.[4] For example, a patent that lists three total inventors, one each from the United States, Canada, and Germany, would be measured as contributing one-third of a patent in each of those countries. The data refer to patent families filed under the Patent Cooperation Treaty within the Five IP Offices (which includes the European Patent Office [EPO]; Japan Patent Office; Korean Intellectual Property Office; National Intellectual Property Administration, PRC; and U.S. Patent and Trade-

[4]See https://www.oecd.org/innovation/inno/keybiotechnologyindicators.htm.

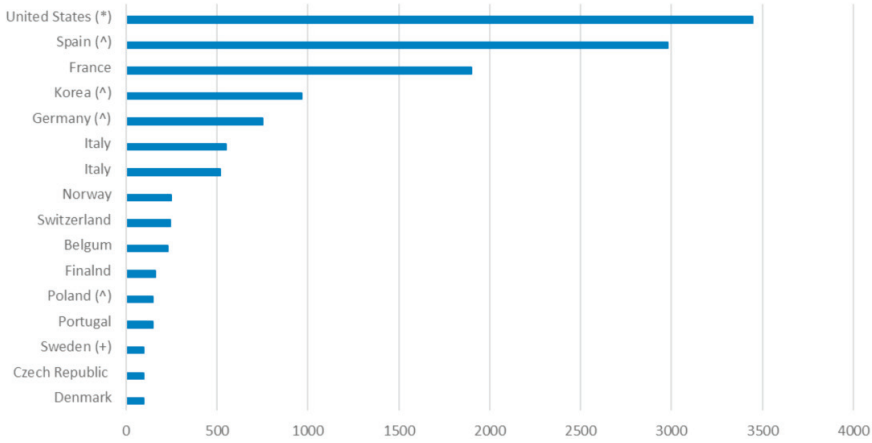


FIGURE 4-10 Number of firms active in biotechnology, 2015.
^ Data for these countries include biotechnology companies, not just biotechnology R&D firms.
+ For Sweden, data include only firms with 10 or more employees.
* For the United States, the number of firms includes only those that actually responded to the survey. The data are adjusted to the weight to account for missing responses. The survey was administered only to firms with five or more employees.
NOTE: Data include biotechnology R&D firms, unless otherwise noted. Data not available for China or Japan. SOURCE: OECD, Key Biotechnology Indicators, http://oe.cd/kbi, updated October 2018.

mark Office [USPTO]), with members filed at the EPO or at the USPTO, by the first filing date. These data document the United States' leadership in biotechnology innovation over the past 20 years, but also the relative erosion of that leadership position. The United States contributed more than 40 percent of patents in 2001, but only slightly more than 35 percent in 2007 and less than 35 percent in 2014. The U.S. percentage is, however, more than twice the fraction contributed by any other country. Japan represents the next-highest fraction of patents at less than 15 percent of the overall total. South Korea and China experienced the greatest increase in the fraction of international biotechnology patents during 2001–2014, with South Korea increasing its fraction from 2 percent to 10 percent and China increasing its fraction from 1 percent to 5 percent.

A different story emerges based on World Intellectual Property data, which compare annual biotechnology patents issued in the United States and China (see Figure 4-13). Unlike the OECD data, these data do not

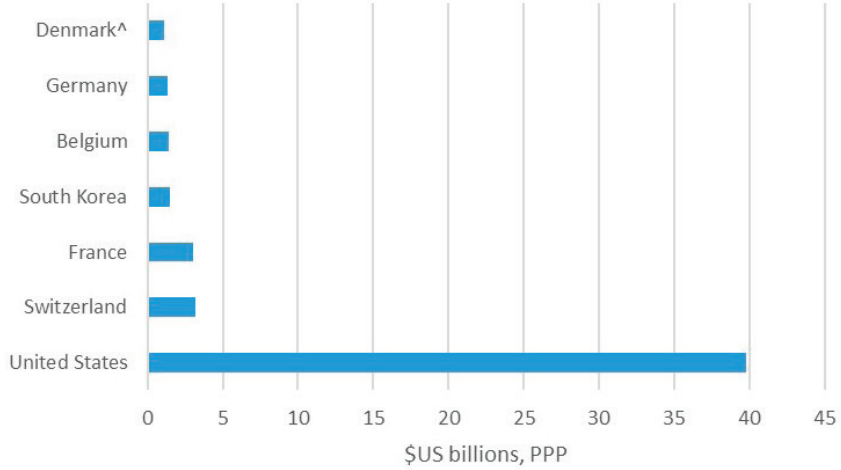


FIGURE 4-11 Biotechnology R&D expenditures in the business sector, 2015. NOTES: Denmark data are from 2013; U.S. data include firms with five or more employees only. SOURCE: OECD, Key Biotechnology Indicators, http://oe.cd/kbi; and OECD, Main Science and Technology Indicators Database, www.oecd.org/sti/msti.htm, updated October 2018.

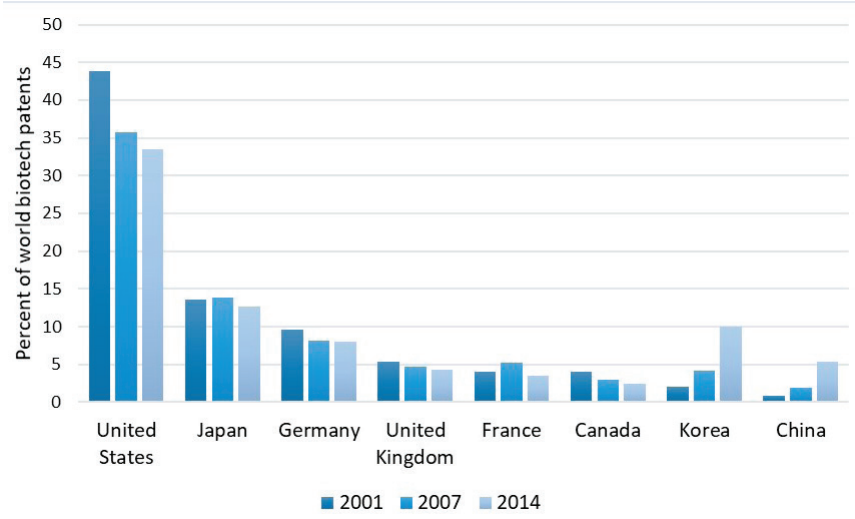


FIGURE 4-12 Fraction of world biotechnology patents, selected countries and years. NOTES: Data: The new list of International Patent Classification codes for defining biotechnology patents was used to extract these data. The definition is outlined in Friedrichs and van Beuzekom (2018). Data refer to patent families filed within the Five IP Offices with members filed at the European Patent Office or at the U.S. Patent and Trademark Office by first filing date and the inventor's residence, using fractional counts. Data for 2014 are estimates. See https://www.oecd.org/innovation/inno/keybiotechnologyindicators.htm.

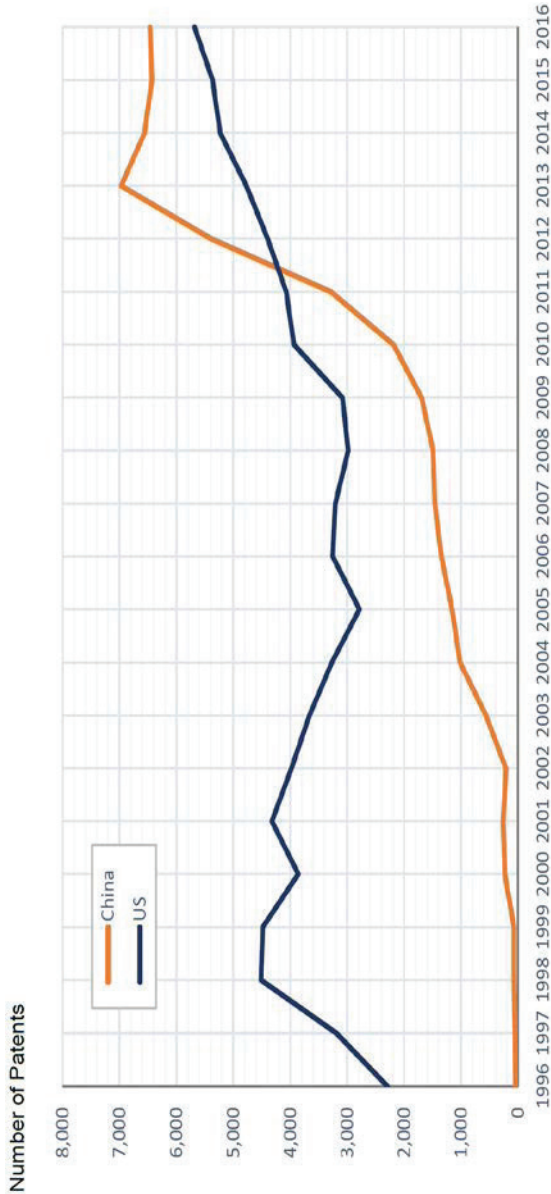


FIGURE 4-13 Annual biotechnology patents granted in the United States and China, 1996–2016.
SOURCE: Gryphon Scientific and Rhodium Group (2019) from World Intellectual Property Organization.

reflect international patents (i.e., patents registered in multiple domains), but rather just patents filed in the United States and China, respectively. These data suggest a substantial increase in biotechnology patenting in China. It is not clear, however, whether these patents reflect innovation at the world's technological frontier, but they may signal China's potential to begin innovating at the world frontier of biotechnology.

More broadly, the extent of commitment by foreign countries to their overall innovation infrastructure and the increasing investments in biosciences by countries, particularly by countries with defined R&D strategies, such as China and South Korea, suggest that U.S. leadership in biosciences and bioeconomy innovation is unlikely to be maintained in the future at the same level as it has been in the recent past.

In terms of the deployment of agricultural biotechnology, the United States leads the world in acreage planted with bioengineered crops, with 40 percent (75.0 million hectares) of the world total in 2017 of 189.8 million hectares. The next four largest shares are in Brazil (26 percent, 50.2 million hectares), Argentina (12 percent, 23.6 million hectares), Canada (7 percent, 13.1 million hectares), and India (6 percent, 11.4 million hectares). Over the first 21 years of the commercialization of bioengineered crops, from 1996 to 2016, the United States captured the largest cumulative economic benefits from the technology (ISAAA, 2017).

NATIONAL COMPARISONS OF ENTREPRENEURSHIP/ VENTURE CAPITAL FUNDING

The entrepreneurial culture of the United States has long been considered an important feature of the national institutional environment, an aspect that has contributed to the nation's technological leadership and economic dynamism. Economists have, however, pointed out that the historical dynamism—such as rate of entrepreneurship, fraction of workers in small and growing firms, and rate of new job creation—that historically characterized the U.S. economy has been showing signs of decline (Decker et al., 2014; Haltiwanger, 2015). While declining dynamism may be an issue in the U.S. economy overall, however, it does not appear to affect the bioeconomy in particular.

There are a number of sources for information on international entrepreneurship and venture funding, but none of them appear to provide consistent, historical data across the full set of sectors encompassed by the bioeconomy. As a result, we surveyed results for several principal bioeconomy sectors and sources, beginning with one of the economically largest sectors of the bioeconomy, biotechnology. The *EY Biotechnology Report 2017* compiles and reports on financing, initial public offerings (IPOs), and venture capital investments based on Capital IQ and VentureSource. These data suggest that the scale of biotechnology venture

financing in the United States continues to greatly exceed that of Europe and leading Asian countries.

Figure 4-14 tracks financing for biotechnology firms in the United States between 2001 and 2016 and demonstrates how venture funding, follow-on funding, and debt funding rose, on average, throughout the 15-year period, while IPO proceeds fluctuated. These patterns are similar to those occurring in the European biotechnology sector during the same period, although of a substantially greater magnitude. Whereas total U.S. biotechnology financing had reached $10 billion by 2003, it did not achieve this level in Europe until 2015 (see Figure 4-15). And although biotechnology ventures in China and South Korea have received substantial investment in the past few years, the data as of 2016 suggest that biotechnology ventures in China, Japan, South Korea, and Taiwan lag substantially behind those in the United States and Europe, having not reached $4 billion in financing in any year prior to or including 2016, the last year of the Ernst and Young (EY) data (see Figure 4-16).

These comparisons rely mainly on venture investment data. Other valuable indicators of competitiveness and leadership in this area would include measures of business dynamics, such as measures of entry (e.g., counts of new firms) and exit (e.g., IPOs, acquisitions, and firm failings).

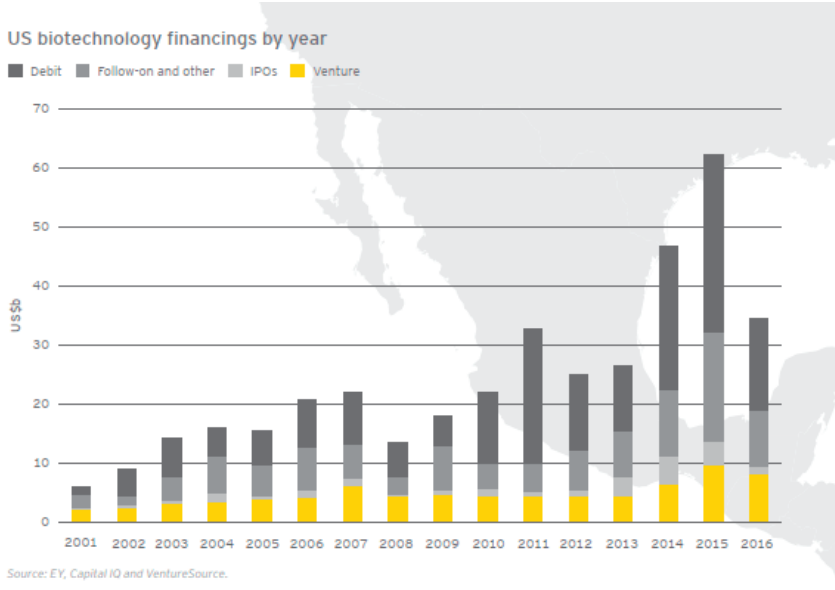


FIGURE 4-14 U.S. biotechnology financings by year, 2001–2016. SOURCE: EY Biotechnology Report 2017, citing Capital IQ, and VentureSource. Reprinted with permission; copyright 2017, Ernst & Young LLP.

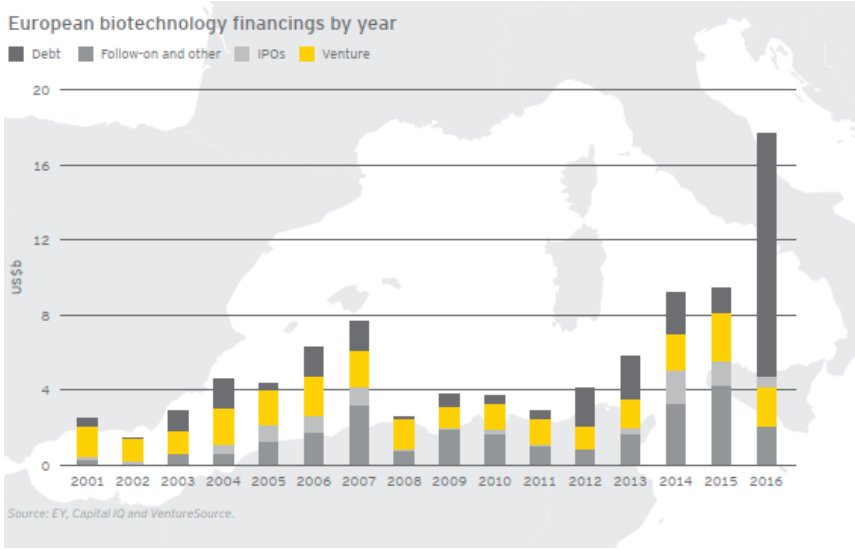


FIGURE 4-15 European biotechnology financings by year, 2001–2016. SOURCE: EY Biotechnology Report 2017, citing Capital IQ, and VentureSource. Reprinted with permission; copyright 2017, Ernst & Young LLP.

U.S. LEADERSHIP CASE STUDY: SYNTHETIC BIOLOGY

Synthetic biology is one of the most dynamic areas of biological science and one of the most interesting emerging subsectors of the bioeconomy. It is also an area in which evidence of U.S. leadership exists in innovation, entrepreneurship, and scientific and economic success. Figure 4-17 reports counts of academic publications in synthetic biology published in journals indexed by Web of Science from 2000 to 2015, showing the worldwide total and the numbers for leading countries by author affiliation. During this period, the number of such publications grew annually from fewer than 200 to more than 1,000. In each year since 2000, the United States has produced more than half of the total global publications in this area.

A University of Manchester and Georgia Tech study by Philip Shapira, Seokbeom Kwon, and Jan Youtie classifies synthetic biology papers indexed by Web of Science that were sponsored by the top 15 synthetic biology funding agencies worldwide based on the agency that originally provided their funding, and derives a series of measures related to these publications (Shapira et al., 2018; see Figure 4-18). Their analyses document that the National Institutes of Health and NSF fund the largest fraction of synthetic biology publications worldwide and that these publications garner more citations than those funded by other agencies. Along with papers funded

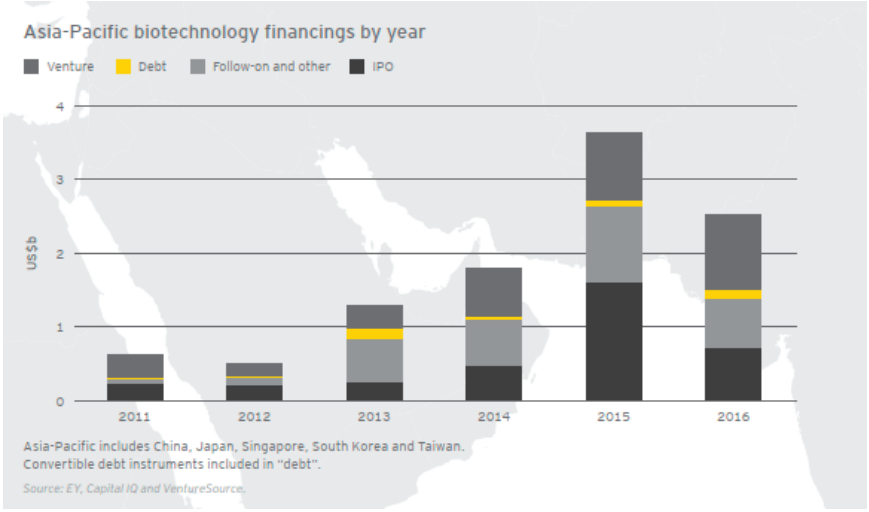


FIGURE 4-16 Biotechnology financings, total across China, Japan, South Korea, and Taiwan, 2011–2016. SOURCE: EY Biotechnology Report 2017, citing Capital IQ, and VentureSource. Reprinted with permission; copyright 2017, Ernst & Young LLP.

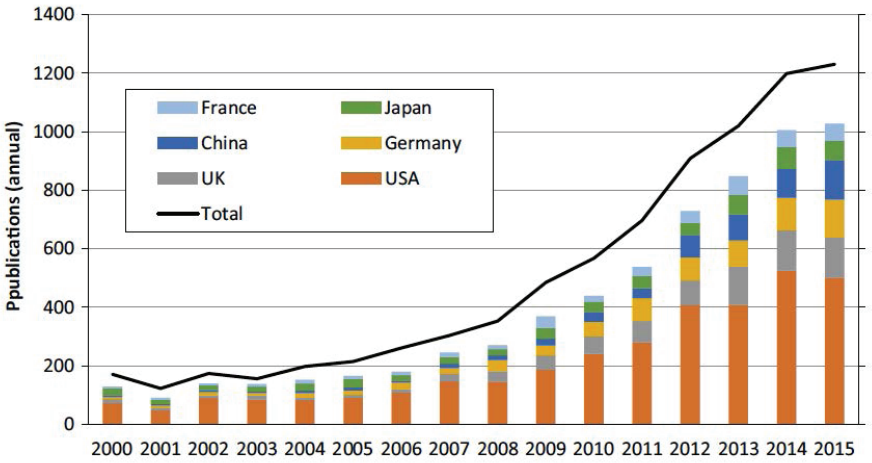


FIGURE 4-17 Synthetic biology publications, worldwide and by leading countries by author affiliation, 2000–2015. NOTE: The line graph depicts worldwide annual publications. The bar chart depicts annual publications for the six leading countries by total publication output. SOURCE: Shapira et al., 2017.

	Funding Agency	Records	Citations	Mean Cites
1	US National Institutes of Health (NIH)	1550	61103	39.4
2	US National Science Foundation (NSF)	1120	31979	28.6
3	China National Natural Science Foundation (NNSFC)	575	6379	11.1
4	European Union	443	11396	25.7
5	UK Biotechnology and Biological Sciences Research Council	369	8375	22.7
6	UK Engineering and Physical Sciences Research Council	314	6321	20.1
7	US Department of Energy (DOE)	282	8522	30.2
8	European Research Council (ERC)	250	4715	18.9
9	Germany Deutsche Forschungsgemeinschaft	235	4905	20.9
10	US Defense Advanced Research Projects Agency	235	8563	36.4
11	China National Basic Research (973) Program	228	3005	13.2
12	US Office of Naval Research	169	7490	44.3
13	Japan Society for the Promotion of Science	158	2095	13.3
14	Canada Natural Sciences and Engineering Research Council (NSERC)	147	2974	20.2
15	Japan Ministry of Education, Culture, Sports, Science and Technology	144	2370	16.5

FIGURE 4-18 Citations to publications sponsored by the top 15 synthetic biology funding agencies, 2000–2015. NOTES: Based on analysis of Web of Science publication records (2000 to mid-July 2018. Shapira et al. (2017) synthetic biology search strategy. N = 11,369 (67% of which report funding acknowledgment information). VantagePoint used for list cleaning of funding agency organizational names. SOURCE: Shapira and Kwon, 2018.

by the U.S. Office of Naval Research, the Defense Advanced Research Projects Agency, and the U.S. Department of Energy, these government-funded papers also receive the highest average number of citations per paper. The National Natural Science Foundation of China funds the third-largest number of synthetic biology papers, but as of 2018, those papers were receiving substantially fewer citations on average relative to those funded by the other agencies tracked by the coauthors. These findings suggest substantial leadership by the United States in the science of synthetic biology. More generally, they suggest the fact that this leadership may be driven, to a significant degree, by investments made by the U.S. federal government.

In further work, Shapira and Kwon (2018) demonstrate the relationship between synthetic biology publications and patents for the 10 countries that generate the largest number of synthetic biology patents (see Figure 4-19). These data, too, document U.S. leadership. Between 2003 and 2017, the authors link more than 4,000 synthetic biology patents to inventors in the United States. The closest country to the United States in the count of patents included in the PATSTAT database (of international patent families) is Japan, which recorded fewer than 1,000 patents during the same period. Authors with affiliations in the United States also published more than 4,000 articles, while the closest country, Great Britain, generated fewer than 1,500. Because these data are based on a longer

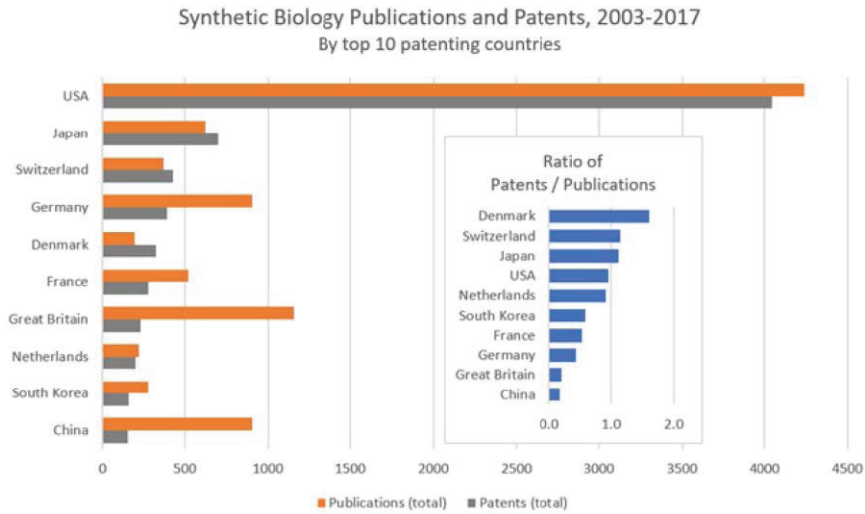


FIGURE 4-19 Synthetic biology publications and patents, 2003–2017. NOTES: Publications: analysis of Web of Science publication records (2000 to mid-July 2018). Shapira et al. (2017) synthetic biology search strategy, *N* = 11,369. Patents: analysis of PATSTAT patent records (2003 to August 3, 2018), *N* = 8,460. Vantage-Point used for data cleaning and analysis. SOURCE: Shapira and Kwon, 2018.

time period, they may underestimate the recent progress made by such countries as South Korea and China; however, the data do make clear the historical leadership of the United States, both in science and in intent to commercialize synthetic biology.

Although the United States maintains a substantial advantage overall in synthetic biology science and innovation, this advantage is not hegemonic. Indeed, the two firms that patent the most in this area are a Danish firm, Novozymes AS, and a Swiss firm, Hoffmann-LaRoche (see Figure 4-20). Headquartered outside of Copenhagen, Denmark, Novozymes is one the world's leading producers of industrial enzymes and microorganisms. Headquartered in Basel, Switzerland, Hoffmann-LaRoche is a global pharmaceutical conglomerate that encompasses multiple R&D centers in the United States, including the main location of initially U.S.-based biotechnology firm Genentech, which has the fourth-highest number of synthetic biology patents identified by Shapira and Kwon (2018) over the period of their study. While 5 of the 6 organizations with the most synthetic biology patents are not based in the United States, 17 of the next 18 are. Overall, more than 60 percent of the 40 organizations with the most synthetic biology patents are based in the United States.

U.S. leadership in synthetic biology is not limited to academia, but appears to extend to entrepreneurship as well. As of early 2019, SynBioBeta had identified more than 350 U.S.-based firms in this subsector, while the countries with the second- and third-most firms, the United Kingdom and France, had only 87 and 27 such firms, respectively (see Figure 4-21). Among the entrepreneurial ventures leveraging synthetic biology in the United States are such firms as Ginkgo Bioworks, which designs microorganisms for commercial use, and two firms funded in 2018—Impossible Foods, which develops plant-based meat substitutes, and Moderna Therapeutics, which develops drug therapies based on messenger RNA.

U.S. LEADERSHIP IN THE BIOECONOMY: SYNTHESIS

Taken together, the data the committee reviewed suggest that the United States is a clear leader in developing research that leads to bioeconomy innovation. The data suggest, however, that other countries, particularly South Korea and China, are increasing their investments in science and innovation.

As is true for other areas of science and innovation, the United States has historically attracted and to a great extent retained the best and the brightest scientific talent to attend its graduate schools, enroll in postdoctoral training, and serve as researchers and faculty. While the data up until 2017 suggest that the United States has continued to attract and retain talented individuals from around the world, scientists and policy makers are beginning to raise questions about the nation's ability to continue

	Assignee	Assignee Type	Country	Patents		Assignee	Assignee Type	Country	Patents
1	NOVOZYMES AS	COMPANY	DK	275	21	MONSANTO TECHNOLOGY LLC	COMPANY	US	51
2	HOFFMANN LA ROCHE	COMPANY	CH	133	22	UNIV PENNSYLVANIA	UNIVERSITY	US	47
3	CELLECTIS	COMPANY	FR	108	23	UNIV TEXAS	UNIVERSITY	US	46
4	GENENTECH INC	COMPANY	US	108	24	GEN HOSPITAL CORP	UNIVERSITY	US	45
5	UNIV KYOTO	UNIVERSITY	JP	105	25	CENTRE NAT RECH SCIENT	GOV NON-PROFIT	FR	44
6	NOVARTIS AG	COMPANY	CH	104	26	DU PONT	COMPANY	US	43
7	MASSACHUSETTS INST TECHNOLOGY	UNIVERSITY	US	103	27	MDRNA INC	COMPANY	US	42
8	DANISCO US INC	COMPANY	US	98	28	MERCK SHARP & DOHME	COMPANY	DK	39
9	DOW AGROSCIENCES LLC	COMPANY	US	91	=29	UNIV LELAND STANFORD JUNIOR	UNIVERSITY	US	38
10	HARVARD COLLEGE	UNIVERSITY	US	88	=29	UNIV OHIO STATE RES FOUND	UNIVERSITY	US	38
11	UNIV CALIFORNIA	UNIVERSITY	US	87	=29	UNIV TOKYO	UNIVERSITY	US	38
12	REGENERON PHARMA	COMPANY	US	85	=32	BIOGEN IDEC INC	COMPANY	US	34
=13	ALNYLAM PHARMACEUTICALS INC	COMPANY	US	84	=32	SCRIPPS RESEARCH INST	GOV NON-PROFIT	JP	34
=13	SANGAMO BIOSCIENCES INC	COMPANY	US	84	=34	BAYER CROPSCIENCE NV	COMPANY	BE	32
15	ISIS PHARMACEUTICALS INC	COMPANY	US	73	=34	DSM IP ASSETS BV	COMPANY	NL	32
16	CHUGAI PHARMACEUTICAL CO LTD	COMPANY	JP	63	36	MODERNA THERAPEUTICS INC	COMPANY	US	31
17	PIONEER HI BRED INT	COMPANY	US	60	37	SANTARIS PHARMA AS	COMPANY	DK	30
=18	AMGEN INC	COMPANY	US	58	=38	AGENCY SCIENCE TECH & RES	GOV NON-PROFIT	SG	28
=18	BROAD INST INC	GOV NON-PROFIT	US	58	=38	CUREVAC GMBH	COMPANY	DE	28
20	GENOMATICA INC	COMPANY	US	53	=38	EVOGENE LTD	COMPANY	IL	28
					=38	JANSSEN BIOTECH INC	COMPANY	US	28

FIGURE 4-20 Top patent assignees in the synthetic biology domain, worldwide, by organization and country of origin, 2003–2018. NOTES: Analysis of PATSTAT patent records (2003 to August 3, 2018), Kwon et al. (2016) synthetic biology patent search strategy, $N = 8,460$ (7,847 with identified assignee country locations). Note that a patent "assignee" is the entity to whom the property right over the patent has been granted. SOURCE: Shapira and Kwon, 2018.

FIGURE 4-21 Global locations of synthetic biology firms. SOURCE: Cumbers, 2019.

to do so, both because of the increasing investments in science by other countries and because of the threats to the historical consensus regarding the national priority of investing in science and innovation in the United States, as discussed in Chapter 7 of this report (Alberts and Narayanamurti, 2019; Kerr, 2019; Peri et al., 2014).

While the overall innovation ecosystem and historical stock of investments protect U.S. leadership in the bioeconomy, a series of other policies and choices that are relevant to future competitive success in this sector deserve consideration both on their merits and with regard to their impact on the bioeconomy. For example, the Information Technology and Innovation Foundation estimated in 2012 that the United States offered R&D tax incentives that were only 27th among the 42 countries it had studied (Stewart et al., 2012). Economists studying tax credits have found evidence that such policies can stimulate R&D investment, and it is possible that greater support[5] for such policies in the United States could contribute to greater bioeconomy competitiveness (Agrawal et al., 2019; Rao, 2016). Given that work characterizing bioeconomies is in a relatively early stage, however, it is likely too soon to make definitive statements about which policy levers have the most influence on bioeconomy leadership. This is particularly true considering the multiple industrial applications for the science and innovation underlying the bioeconomy. The committee hopes that research efforts will engage with these topics.

CONCLUSIONS

This chapter has examined the available data to assess the status of U.S. leadership within the global bioeconomy, providing a discussion of the strengths and caveats of each metric.

Conclusion 4-1: The United States is a clear leader in the global landscape in multiple areas related to the bioeconomy, including federal funding for biological sciences; the production of science, innovation, and entrepreneurship in synthetic biology; and the generation and adoption of bioengineered crops. This leadership has been based to a substantial degree on the country's historical edge in science and the production of new-to-the-world knowledge.

Conclusion 4-2: The current U.S. international position is one of general leadership in those areas built on research and development in the life sciences—leadership that has been built as a result of and not

[5]It should be noted that the U.S. R&D tax credit was made permanent in 2015. However, it was not changed in magnitude (https://www.eidebailly.com/insights/articles/rd-tax-credit-enhanced-and-becomes-permanent).

despite, open scientific borders. Continued leadership will involve (1) careful analysis of the policies and ecosystem features that undergird the bioeconomy, and (2) continued commitment from the federal government to world-leading investment in sciences.

REFERENCES

Agrawal, A., C. Rosell, and T. S. Simcoe. 2019. *Tax credits and small firm R&D spending*. NBER working paper 20615. https://www.nber.org/papers/w20615 (accessed September 7, 2019).

Alberts, B., and V. Narayanamurti. 2019. Two threats to U.S. science. *Science* 364(6441):613.

American Academy of Arts & Sciences. 2014. *Restoring the foundation: The vital role of research in preserving the American dream*. https://www.amacad.org/publication/restoring-foundation-vital-role-research-preserving-american-dream (accessed September 7, 2019).

Cho, S. W., S. Kim, J. M. Kim, and J. S. Kim. 2013. Targeted genome engineering in human cells with the Cas9 RNA-guided endonuclease. *Nature Biotechnology* 31(3):230–232.

Cong, L., F. A. Ran, D. Cox, S. Lin, R. Barretto, N. Habib, P. D. Hsu, X. Wu, W. Jiang, L. A. Marraffini, and F. Zhang. 2013. Multiplex genome engineering using CRISPR/Cas systems. *Science* 339(6121):819–823.

Cumbers, J. 2019. *Defining the bioeconomy*. Presentation to the Committee on Safeguarding the Bioeconomy. January 28. http://nas-sites.org/dels/studies/bioeconomy/meeting-1 (accessed March 10, 2020).

de Solla Price, D. 1976. An extrinsic value theory for basic and "applied" research. *Policy Studies Journal* 5:160–168.

Decker, R., J. Haltiwanger, R. Jarmin, and J. Miranda. 2014. The role of entrepreneurship in U.S. job creation and economic dynamism. *Journal of Economic Perspectives* 28(3):3–24.

Doudna, J. A., and E. Charpentier. 2014. Genome editing: The new frontier of genome engineering with CRISPR-Cas9. *Science* 346(6213):1258096.

EY Biotechnology Report. 2017. Ernst & Young LLP. https://www.ey.com/Publication/vwLUAssets/ey-biotechnology-report-2017-beyond-borders-staying-the-course/$FILE/ey-biotechnology-report-2017-beyond-borders-staying-the-course.pdf (accessed August 1, 2019).

Friedrichs, S., and B. van Beuzekom. 2018. Revised proposal for the revision of the statistical definitions of biotechnology and nanotechnology. OECD Science, Technology and Industry Working Papers, No. 2018/01, OECD Publishing, Paris, https://doi.org/10.1787/085e0151-en.

Furman, J. L., and R. Hayes. 2004. Catching up or standing still?: National innovative productivity among "follower" countries, 1978–1999. *Research Policy* 33(9):1329–1354.

Furman, J. L., M. E. Porter, and S. Stern. 2002. The determinants of national innovative capacity. *Research Policy* 31(6):899–933.

Garfield, E. 1979. 2001: An information society? *Journal of Information Science* 1(4):209–215.

Gryphon Scientific and Rhodium Group. 2019. *China's biotechnology development: The role of U.S. and other foreign engagement.* https://www.uscc.gov/sites/default/files/Research/US-China%20Biotech%20Report.pdf (accessed September 7, 2019).

Haltiwanger, J. 2015. *Top ten signs of declining business dynamism and entrepreneurship in the U.S*. http://econweb.umd.edu/~haltiwan/haltiwanger_kauffman_conference_august_1_2015.pdf (accessed September 7, 2019).

ISAAA (International Service for the Acquisition of Agri-biotech Applications). 2017. *Global status of commercialized niotech/GM crops in 2017: Biotech crop adoption surges as economic benefits accumulate in 22 years*. ISAAA brief no. 53. Ithaca, NY: ISAAA.

Jinek, M., K. Chylinski, I. Fonfara, M. Hauer, J. A. Doudna, and E. Charpentier. 2012. A programmable dual-RNA-guided DNA endonuclease in adaptive bacterial immunity. *Science* 337(6096):816–821.

Kerr, W. 2019. *The gift of global talent*. Palo Alto, CA: Stanford Press.

Krugman, P. 1991. Increasing returns and economic geography. *Journal of Political Economy* 99(3):483–499.

Kwon, S., J. Youtie, and P. Shapira. 2016. *Building a patent search strategy for synthetic biology.* Working paper. Atlanta, GA: Tech Program in Science, Technology and Innovation Policy. http://bit.ly/2E3Py7T (accessed September 1, 2019).

Leydesdorff, L. 2001. Scientometrics and Science Studies. *Bulletin of Sociological Methodology/ Bulletin de Méthodologie Sociologique* 71(1):79–91.

Mali, P., L. Yang, K. M. Esvelt, J. Aach, M. Guell, J. E. DiCarlo, J. E. Norville, and G. M. Church. 2013. RNA-guided human genome engineering via Cas9. *Science* 339(6121):823–826.

McNutt, M. K. 2019. *Maintaining U.S. leadership in science and technology*. Statement before the Committee on Science, Space, and Technology, U.S. House of Representatives, March 6. http://www8.nationalacademies.org/onpinews/newsitem.aspx?RecordID=362019b (accessed September 7, 2019).

Murmann, J. P. 2003. *Chemicals and long-term economic growth: Insights from the chemical industry*. Cambridge, UK: Cambridge University Press.

NAS/NAE/IOM (National Academy of Sciences, National Academy of Engineering, and Institute of Medicine). 2010. *Rising above the gathering storm, revisited: Rapidly approaching category 5*. Washington, DC: The National Academies Press. doi: 10.17226/12999.

NRC (National Research Council). 2007. *Rising above the gathering storm: Energizing and employing America for a brighter economic future*. Washington, DC: The National Academies Press. doi: 10.17226/11463.

NSB and NSF (National Science Board and National Science Foundation). 2018. *2018 Science & Engineering Indicators*. https://www.nsf.gov/statistics/2018/nsb20181/assets/nsb20181.pdf (accessed September 11, 2019).

Peri, G., K. Shih, C. Sparber, and A. M. Zeitlin. 2014. *Closing American Doors*. New York: Partnership for a New American Economy.

Qi, L. S., M. H. Larson, L. A. Gilbert, J. A. Doudna, J. S. Weissman, A. P. Arkin, and W. A. Lim. 2013. Repurposing CRISPR as an RNA-guided platform for sequence-specific control of gene expression. *Cell* 152(5):1173–1183.

Rao, N. 2016. Do tax credits stimulate R&D spending? The effect of the R&D tax credit in its first decade. *Journal of Public Economics* 140:1–12.

Schoenbach, U. H., and E. Garfield. 1956. Citation Indexes for Science. *Science* 123(3185):61–62.

Shapira, P., and S. Kwon. 2018. Synthetic biology research and innovation profile 2018. *Publications and Patents*. doi: 10.1101/485805.

Shapira, P., S. Kwon, and J. Youtie. 2017. Tracking the emergence of synthetic biology. *Scientometrics* 112:1439–1469.

Simkin, M. V., and V. P. Roychowdhury. 2003. Read before you cite! *Complex Systems* 14:269–274.

Slaymaker, I. M., L. Gao, B. Zetsche, D. A. Scott, X. Winston, W. X. Yan, and F. Zhang. 2016. Rationally engineered Cas9 nucleases with improved specificity. *Science* 351(6268):84–88.

Stewart, L. A., J. Warda, and R. D. Atkinson. 2012. *We're #27!: The United States lags far behind in R&D tax incentive generosity.* Washington, DC: Information Technology and Innovation Foundation.

Suzuki, K., Y. Tsunekawa, R. Hernandez-Benitez, J. Wu, J. Zhu, E. J. Kim, F. Hatanaka, M. Yamamoto, T. Araoka, Z. Li, M. Kurita, T Hishida, M. Li, E. Aizawa, S. Guo, S. Chen, A. Goebl, R. D. Soligalla, J. Qu, T. Jiang, X. Fu, M. Jafari, C. R. Esteban, W. T. Berggren, J. Lajara, E. Nuñez-Delicado, P. Guillen, J. M. Campistol, F. Matsuzaki, G. H. Liu, P. Magistretti, K. Zhang, E. M. Callaway, K. Zhang, and J. C. Belmonte. 2016. In vivo genome editing via CRISPR/Cas9 mediated homology-independent targeted integration. *Nature* 540:144–149.

PART II

UNDERSTANDING THE ECOSYSTEM AND IDENTIFYING NEW TRENDS IN THE U.S. BIOECONOMY

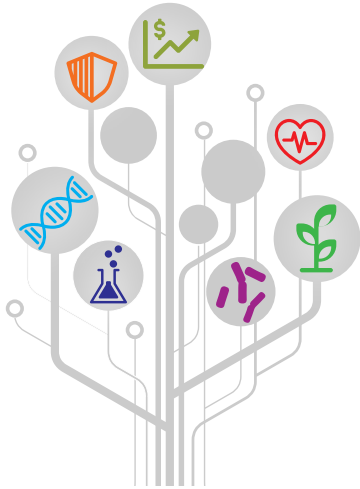
Having articulated the committee's definition for the U.S. bioeconomy and having compiled and analyzed the data available for assessing its value and its leadership position within the global bioeconomy, the report turns in Part II to examining the ecosystem in which the U.S. bioeconomy operates and methods for horizon scanning that can be used to identify new technologies, markets, and data sources with potential to drive the bioeconomy's future development.

Chapter 5 begins by reviewing the overall U.S. system in which life sciences research is conducted and translated into innovative products and services. It covers the surrounding ecosystem—including regulatory and intellectual property regimes, investment sources, and workforce policies and structures—that fosters and supports the U.S. bioeconomy. This chapter serves as a basis for more in-depth discussions related to potential risks and associated policy gaps in subsequent chapters, recognizing that an understanding of the ecosystem is required for identifying potential risks. This chapter also explores a number of trends and innovations that are shaping and altering how the U.S. life sciences system functions.

Chapter 6 examines the various methodologies for conducting horizon-scanning and foresight activities, with a focus on applying horizon scanning as a policy tool. This chapter directly addresses the final element of the committee's Statement of Task by examining best practices in horizon scanning and foresight. It articulates the steps needed to identify key elements of the process, considers how to optimize a horizon scan, and

examines past examples. This chapter also provides case studies related to the bioeconomy that can aid in identifying issues, examples of horizon scanning conducted by different government agencies, and examples focused on different application areas (e.g., health, food safety, and the environment). Finally, this chapter reviews tools for future thinking that can be used in conjunction with a horizon scan.

These two chapters move the discussion forward by describing the dynamic system in which the U.S. bioeconomy operates and providing decision makers with a set of tools with which to anticipate and respond to changes and advances in the U.S. bioeconomy.



5 THE ECOSYSTEM OF THE U.S. BIOECONOMY

Summary of Key Findings

- The U.S. bioeconomy relies on a complex and evolving ecosystem that extends from research and development through manufacturing, and it also encompasses related services.
- The U.S. bioeconomy draws on multiple resources and encompasses multiple applications. As a result, all regions of the United States have strengths that contribute to the bioeconomy.
- The impacts within the U.S. bioeconomy of investments that support fundamental research and the development of enabling technologies are nonlinear. These impacts cannot necessarily be predicted when initial investments are made.
- The bioeconomy is an increasingly data-driven enterprise. The development of diagnostics, drugs, synthetic biology products, and more benefits from access to information resources.
- A number of policies and practices support the U.S. bioeconomy, directed at achieving (1) a predictable and responsive regulatory environment; (2) a skilled workforce; (3) investments at multiple stages, from research to commercialization, and strategies for taking precompetitive interests of industry into account; and (4) the targeted use of incentives and market pull.

This chapter begins by reviewing innovation in the bioeconomy from research to commercial application, describing the overall U.S. system in which life sciences research is conducted and translated into innovative products and services. It then details characteristics of the surrounding ecosystems that support the U.S. bioeconomy—including regulatory and intellectual property regimes, investment sources, and workforce policies and structures. The third section of the chapter explores a number of trends and changes that are shaping and altering how the bioeconomy functions and looks ahead to the need to keep abreast of emerging trends and to undertake strategic planning. This is followed by discussion of one tool for strategic planning in support of the U.S. bioeconomy: the use of the Technology Readiness Level (TRL) scale. Throughout the chapter, selected examples of developments that are helping to power the life sciences innovation pipeline are highlighted to showcase key messages. The chapter ends with the committee's conclusions with respect to discovery and innovation in the U.S. bioeconomy.

INNOVATION IN THE BIOECONOMY: FROM RESEARCH TO APPLICATION

As discussed in Chapter 3 (see Box 3-1) and defined by the Organisation for Economic Co-operation and Development (OECD), innovation is "a new or improved product or process (or combination thereof) that differs significantly from the unit's previous products or processes and that has been made available to potential users (product) or brought into use by the unit (process)" (OECD/Eurostat, 2018, p. 20). A similar definition is used by the National Science Foundation (NSF) in *Science and Engineering Indicators 2018* (NSB and NSF, 2018). As the pace of scientific discovery has accelerated and discoveries have evolved into practical applications for commercial products and services, the United States has realized the benefits of a national innovation ecosystem capable of transforming research discoveries into economic and societal benefits. This ecosystem is essential to the continued realization of such benefits to the United States. For the bioeconomy, the system that enables this innovation is built on fundamental advances in basic biological knowledge in concert with the continued creation and maturation of enabling platform technologies, which together are translated to meaningful application and deployed commercially (see Figure 5-1). This section reviews the role of scientific discovery and basic research, the contributions of enabling technologies, and the general process of translation and commercialization.

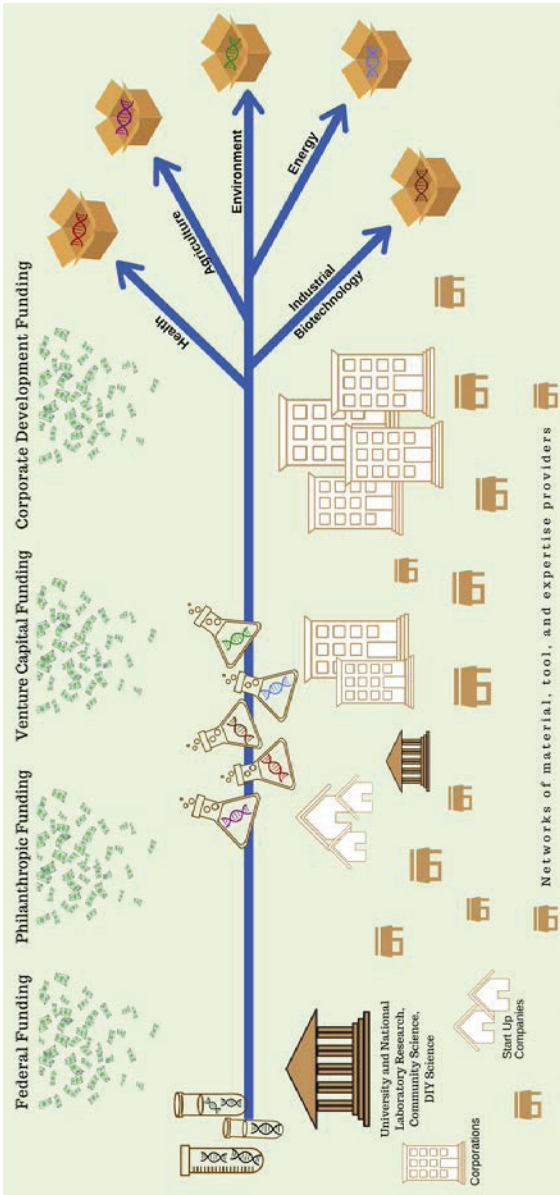


FIGURE 5-1 Advances in fundamental biological knowledge and in a number of enabling technologies are creating commercial opportunities with application to many sectors of the bioeconomy. An idea moves from the basic research and proof-of-concept stages (left), through further development and scale-up (middle), to commercial deployability (right). This path is not necessarily a linear one, and it involves multiple stakeholders from traditional and nontraditional research communities; start-up companies; commercial entities; and networks of providers supplying materials, tools, and expertise. Federal sources generally provide support for the earlier stages of these pathways and can be supplemented with philanthropic support, with venture capital investment and commercial funding supporting later stages in the process. Translation into commercial products does not necessarily happen on identical timescales for applications in the health, agriculture, environment, energy, and industrial biotechnology sectors, represented by branching points along the pathway (illustrative only).

The Role of Scientific Discovery and Basic Research

For decades, the United States has led the world in investment and activity in basic life sciences research (see Chapter 4). Supported by federal funding for world-class universities, research nonprofits, and federal research laboratories, the nation's life sciences research enterprise has helped create the foundation for discovery that is required to realize benefits across a variety of applications in health, agriculture, environment, energy, and industrial biotechnology (see Chapter 3 for detail on data and measurement strategies for capturing the scope of the U.S. bioeconomy). While it continues to be impossible to predict the nature and timing of the next significant basic research breakthrough, it is clear that the pace of knowledge accumulation is accelerating (IAC, 2014). For example, as of 2015, the amount of DNA sequence data produced was doubling every 7 months (Stephens et al., 2015).

Early-stage discovery often derives from public investment in research and in the training of scientists to seed the next-generation workforce. Although the value and importance of investment in basic scientific discovery have been known since early in the country's history, Vannevar Bush articulated the importance of scientific research to national security and economic well-being in the letter of transmittal to President Roosevelt of his 1945 report *Science, the Endless Frontier: A Report to the President*: "Scientific progress is one essential key to our security as a nation, to our better health, to more jobs, to a higher standard of living, and to our cultural progress" (Bush, 1945, p. 2). One of the most exciting aspects of scientific research is that the process often begins with attempts to explore the natural world with the goal of understanding some of the principles that govern it. As scientific knowledge is gained, however, opportunities are created to use that knowledge for a variety of applications—to solve problems that previously could not have been solved; to create technologies that previously had not been imagined; and to create businesses in areas that previously had not been developed. In some cases, these benefits are reaped quickly, while in other cases, the benefits of the practical application of scientific knowledge take years or decades to be realized. Nonetheless, a signature feature of basic scientific research is that discoveries can be based on sometimes indirect, unpredictable, serendipitous events. In many such cases, the research has led to significant economic outcomes (see Box 5-1).

Progress in biological discovery has also been rooted in the culture of science and reliance on fundamental principles that help advance the state of knowledge. These principles include respect for the integrity of knowledge, collegiality, honesty, objectivity, and openness (NRC, 1992), as well as recognition of the importance of adhering to rigorous scientific

BOX 5-1
Important Outcomes Resulting from Fundamental Research

Prominent examples of how investment in basic research can lead to broad-based impacts across diverse application areas are articulated by the Nobel Prizes. One such example illustrates how investment in basic biology research can result in diverse applications. Dr. Edmond Fisher was awarded the 1992 Nobel Prize in Physiology or Medicine (with Edwin Krebs) for his discoveries concerning reversible protein phosphorylation as a biological regulatory mechanism. Fisher's work, which was supported by the National Science Foundation (NSF) in the 1970s,[a] helped uncover the paradigm of phosphorylation–dephosphorylation using kinase/phosphatase enzymes that regulate many aspects of eukaryotic cells. These processes play critical roles in controlling how human, plant, and yeast cells grow, metabolize nutrients, and respond to changes in their environments, and Fisher's work paved the way for understanding the biology underpinning the development of medicines, the growth of plants and animals, and the use of biology to create biofuels.

Another example of how a life science–based technological paradigm can have significant economic impact in a range of sectors is the work of Dr. Frances Arnold, who was awarded the 2018 Nobel Prize in Chemistry (shared with Dr. George Smith and Dr. Gregory Winter). Her work on the directed evolution of enzymes was supported by several NSF awards, including a Presidential Young Investigator Award in 1989.[b] Arnold developed an approach to evolving enzymes in the laboratory to confer new or improved properties compared with those found in nature. This paradigm has been used to develop enzymes capable of synthesizing new molecules, new routes to biofuels, enzymes used in laundry detergents, and medicines for treating type 2 diabetes. Arnold's approaches are being used broadly by both academic scientists trying to understand basic biological phenomena and industrial scientists bringing new products to market.

---

[a]See https://www.nsf.gov/news/special_reports/nobelprizes/med.jsp.
[b]See https://www.nsf.gov/news/special_reports/nobelprizes/che.jsp.

methods. The presentation of research results at conferences and the publication of results in the peer-reviewed literature have also been important mechanisms for the diffusion of information and methods, as well as advancement in the field. The increasing use of prepublication servers, such as BioRxiv, and rapid communication on other Internet platforms are now providing speedier access to information in an increasingly global context.

Biological research has benefited greatly from the open sharing of information, particularly in the genomics era. Such resources as GenBank, supported by the National Institutes of Health (NIH) (and coordinated with international partners such as the DNA DataBank of Japan and the European Nucleotide Archive), provide free access to hundreds of

millions of DNA sequences.[1] Physical repositories such as Addgene offer access to plasmids developed by researchers for dissemination to the broader life sciences community.[2] Open-source software enables bioinformaticians to mix and match compatible tools in order to customize the analysis of biological data, particularly next-generation sequencing data (Carrico et al., 2019). Data scientists in all disciplines have benefited from the development and sharing of data and software for statistical analysis and machine learning; with the advent of "-omics" technologies, such as genomics and metabolomics, these tools are increasingly applied to biology. A previous report of the National Academies titled *Open Science by Design* notes that "openly sharing articles, code, and data in all phases of the research process is beneficial to the research community, to the broader scientific establishment, to policy makers, and to the public at large" (NASEM, 2018d, p. 107).

America's life science research base is also amplified, and the pace of discovery is augmented, by efforts undertaken in other research-intensive countries, including China, Germany, Switzerland, and the United Kingdom, among others. The increasing extent to which scientific collaborations are global will shape progress in scientific discovery and translation in ways that are positive for the United States, as well as in ways that may pose challenges (see Chapter 7).

The Contribution of Enabling Technologies

In the life science research and innovation enterprise, basic discoveries are often accelerated by enabling technologies. Some enabling technologies (such as next-generation DNA sequencing technology or advanced genome-editing tools) are derived directly from the life sciences community, while others (such as automated liquid handling or machine learning algorithms for data analysis and inference) are derived from parallel communities and can also serve to benefit life sciences research and innovation. In an academic setting, this is manifested in the rise of core facilities that purchase, operate, and maintain specialized equipment, such as DNA sequencers, confocal microscopes, or mass spectrometers, that would otherwise be too costly for individual laboratories to purchase (Hockberger et al., 2018). High-performance computing services are also becoming available as core facilities (Courneya and Mayo, 2018). In many cases, these enabling technologies can drive the development of for-profit or not-for-profit businesses. Contract research laboratories see continued

[1]See https://www.ncbi.nlm.nih.gov/genbank/statistics.
[2]See https://www.addgene.org.

growth and can provide commodity as well as specialized services for customers (Nature Biotechnology, 2014).

Translation and Commercialization

As a given scientific community continues to mature in its understanding of basic research discoveries, opportunities arise that permit practical application of those discoveries. In the life sciences, multiple application areas including human health, agriculture, energy, industrial biotechnology, and the environment are relevant to the bioeconomy. In some cases, diverse applications can arise in the context of a particular biological discovery. For example, understanding of how cells grow can impact understanding of cancer and cancer treatments in human cells, of crop yields in plants, of assisted reproduction techniques in cattle, of remediation of environmental contaminants, or of certain types of bacteria as sustainable energy sources. It is worth noting, however, that the timescale associated with meaningful translation of basic life science discoveries into practical application can differ based on the type of organism and application area.

In the process of translation of a discovery to commercialization, a middle stage of activity occurs, often called the "valley of death," that is considered high-risk applied research. Frequently, this research is considered too applied by funders of the basic research classically pursued by universities and is too high risk to receive attention from industry for its commercial application. Strategies for reducing this gap, including public–private partnerships and venture capital investment, can be useful in stimulating innovation. In the later stages of development pathways, as the science and technology that underlie a potential new product or service matures, the for-profit sector often drives the advances, motivated by commercial opportunities.

THE SURROUNDING ECOSYSTEM SUPPORTING THE U.S. BIOECONOMY

The U.S. bioeconomy depends on a web of federal agencies that support life sciences research. Federal and private investments catalyze and support the bioeconomy from basic science to commercialization. They include investments for intellectual property (IP) protections and regulatory frameworks that can capture returns on innovation while protecting the health and safety of people and the environment. Investments in the bioeconomy also serve to develop the necessary skilled workforce. Efforts directed to scientific and technical standards development and the use of market incentives such as government purchasing programs also contribute. This section introduces a variety of U.S. agencies, policies, and

mechanisms that help in realizing the potential of scientific and technical advances and that function to support the U.S. bioeconomy.

Federal Agencies Addressing Aspects of Life Sciences Research

At least 25 agencies and departments support research and development (R&D) in areas of the life sciences (see Box 5-2, which lists the agencies and departments involved in preparations for the 2012 National Bioeconomy Blueprint). A number of additional departments have roles related to the bioeconomy and could be added to this list, including the Biomedical Advanced Research and Development Authority, U.S. Centers for Medicare & Medicaid Services, U.S. Army Research Office, U.S. Air Force Office of Scientific Research, U.S. Army Combat Capabilities Development Command, U.S. Department of Justice, and National Park Service. These agencies play key roles in supporting both basic research and discovery and translational activities within the scope of their missions, and many also support R&D in converging areas of science and technology that contribute to the bioeconomy. Given the diversity of federal stakeholders, no single agency has a clear lead in advancing U.S. bioeconomy goals. Sustaining the U.S. life sciences enterprise and advancing the U.S. bioeconomy will thus require the engagement of multiple agencies and departments across the government.

Investments That Catalyze and Support the Bioeconomy

Government Support of Research and Development

Government R&D investments include fundamental research in biological sciences and enabling technologies, as well as investments targeted more directly in areas of biotechnology that can meet specific needs of the bioeconomy and that support specific missions of government agencies, such as the U.S. Department of Defense. Advances in the bioeconomy can also be supported by shared use of unique government R&D facilities and collaboration between government researchers and private-sector entities through the use of cooperative research and development agreements, as well as the encouragement of industrial consortia by which private firms work together to develop precompetitive technologies and supporting data. In addition, programs specifically targeted to promote small businesses' development of technologies with the potential for commercialization, such as the Small Business Innovation Research and the Small Business Technology Transfer programs, can facilitate the transition from research to product by reducing barriers and accelerating translation (Link and Morrison, 2019; Narayanan and Weingarten, 2018).

BOX 5-2
Examples of Federal Departments and Agencies That Support Biological Research

National Aeronautics and Space Administration

National Science Foundation

Smithsonian Institution

U.S. Agency for International Development

U.S. Department of Agriculture
- Agricultural Research Service
- Forest Service
- National Institute of Food and Agriculture

U.S. Department of Commerce
- National Institute of Standards and Technology
- National Oceanic and Atmospheric Administration

U.S. Department of Defense
- Defense Advanced Research Projects Agency
- Defense Science and Technology Program
- Office of Naval Research
- U.S. Army Medical Research and Materiel Command

U.S. Department of Energy
- Advanced Research Projects Agency–Energy
- Office of Science
- Office of Energy Efficiency and Renewable Energy

U.S. Department of Health and Human Services
- National Institutes of Health
- Office of the Assistant Secretary for Preparedness and Response
- U.S. Centers for Disease Control and Prevention
- U.S. Food and Drug Administration

U.S. Department of Homeland Security
- Science and Technology Directorate

U.S. Department of the Interior
- Fish and Wildlife Service
- U.S. Geological Survey

U.S. Department of Veterans Affairs

U.S. Environmental Protection Agency

SOURCE: White House, 2012.

Private Investments That Support the Bioeconomy, Including Venture Capital and Public–Private Partnerships

Support for early-stage research is essential for the discovery of new knowledge and the development of a trained talent pool, and as a catalyst for opportunities for innovation. This support, primarily from government sources and sometimes by private foundations, can establish proof of concept for new ideas and technologies. However, the endpoint of this basic research phase is typically too early in the maturation of a technology for it to move into the marketplace as a new product or service. At least two sources of investment support businesses seeking to mature technologies into commercial products and processes: the venture capital community and public–private partnerships.

The venture capital community provides critical funding to help early-stage businesses advance and develop their technologies into products. By providing cash, typically in exchange for equity and other considerations, the venture capital community can provide significant financial resources that help companies cross the valley of death, creating significant value for the investors (which often means relying on a few large payoffs to cover losses) while bringing new products and services to the market (Bristow et al., 2018; see also the assessment of metrics of U.S. leadership in Chapter 4). The world-leading entrepreneurial ecosystem in the United States contributes to economic growth (WEF, 2018) and is one of key pillars of the U.S. bioeconomy.

A large number of public–private partnerships result from efforts to bring stakeholders from the federal government together to work collaboratively and interactively with small, medium, and large companies; academia; and other nonprofits to help bring new technologies to the market. One example is the Manufacturing USA program,[3] a collection of 14 manufacturing institutes, each a public–private partnership funded jointly by government, industry, and nonprofits that work to develop and advance manufacturing-related technologies. Several of these institutes, including those working on biofabrication and regenerative medicine, biopharmaceuticals, robotics, and digital technologies, connect directly to the bioeconomy.[4] The program also brings together a broad cross-section of relevant government organizations, including the U.S. Departments of Agriculture, Commerce, Defense, Education, Energy, Health and Human Services, and Labor; the National Aeronautics and Space Administration (NASA); and NSF.

[3]See www.manufacturingusa.com.

[4]Examples include the Advanced Regenerative Manufacturing Institute (BioFabUSA), the National Institute for Innovation in Manufacturing Biopharmaceuticals, the Advanced Robotics for Manufacturing Institute, and Manufacturing Times Digital.

Another relevant class of public–private partnerships is created through the Foundation for the National Institutes of Health (FNIH). FNIH, established by Congress in 1990,[5] serves to accelerate biomedical research by forging collaborations among NIH and public and private institutions. As a complement to efforts focused on developing a given technology past the valley of death, FNIH activities typically focus on large-scale programs for which broad-based expertise and engagement can create new precompetitive knowledge. For example, the Accelerating Medicines Partnership program has provided new technologies to speed up drug discovery for rheumatoid arthritis, lupus, diabetes, Alzheimer's disease, and Parkinson's disease (Dolgin, 2019).

Private investment has an important role as a driving force in the bioeconomy, and the value of public–private partnerships that can seed new innovation or bring stakeholders together to address the valley of death of technologies is clear. As these models expand around the world, it will be important for the United States to continue to nurture and support such efforts, as well as to identify new means and opportunities for stimulating the bioeconomy.

Support for Intellectual Property Rights

Biotechnology is one of the most research-intensive industries, and biotechnology companies must bear significant costs in bringing new products to market. Although extensive research time is needed for biotechnology companies to develop new products and processes, copying of those products and processes (by potential competitors, for example) is relatively inexpensive. For this reason, biotechnology companies often seek to protect the results of their research by securing IP rights that can provide the exclusivity needed to protect their investments.

Of the many forms of IP, patents and trade secrets are the two most commonly used by biotechnology companies to protect their innovations (Sherkow, 2016; see Box 7-2 in Chapter 7). Patents allow companies to prevent competitors from using their innovations, but offer only a limited period of exclusivity (typically 20 years from the date of filing), after which the technology described in the patent enters the public domain (Title 35 of the U.S. Code—Patents; NRC, 2004). Trade secrets, by comparison, can last indefinitely, but will not prevent a competitor from reverse engineering or independently discovering an innovation. Both mechanisms can be used strategically to help companies maintain their competitive advantage, and thereby contribute to the companies' economic success and to the bioeconomy as a whole.

[5]See www.fnih.org.

Recognizing the importance of the exclusivity provided by patents, Congress passed the Bayh–Dole Act of 1980, which vested patent rights to technologies and inventions developed with federal funding in their nongovernmental developers.[6] One purpose of this legislation was to encourage universities and nonprofit research institutions to patent and license their innovations as a means of motivating private-sector companies to make further investments in commercializing innovations that would not be viable without exclusive rights. There has since been a dramatic increase in university patenting and licensing activity, although the effectiveness of the Bayh–Dole Act in encouraging technology transfer remains a matter of debate (NRC, 2011; NSB and NSF, 2018). Of note, a recent study by the National Institute of Standards and Technology (NIST) identified a number of strategies that would improve federal technology transfer policies and practices without requiring legislative changes to the Bayh–Dole Act (NIST, 2019). Although global investment in biotechnology remains strong,[7,8] investment in the life sciences has been negatively affected by the increased uncertainty over the patent eligibility of biotechnology innovations. (See the discussion of the risks posed by an ineffective or inefficient IP environment in Chapter 7.) As a result, biotechnology companies are exploring mechanisms outside the U.S. patent system that could support their investments in R&D of their innovations.

As an example, at least one company has sought copyright protection for nucleotide sequences (Holman, 2017). Copyright protects the expression of ideas (or, more formally, works of authorship fixed in a tangible medium of expression)[9] and can be used to protect software and data analytic tools that contribute to research and commercial translation. In the United States, however, there is currently no legislative or judicial support for copyright protection of biological sequences, and attempts to register nucleotide sequences with the U.S. Copyright Office have failed (Burk, 2018). If extended to biological sequences, copyright protection could enable open-source licensing models, but copyright would offer only shallow use protections for biological innovations while being difficult to enforce (Torrance and Kahl, 2014).

Regulatory exclusivity is another strategy enabling companies to capture benefits from innovation, offering a limited term of exclusivity in

[6]Bayh–Dole Act—Patent and Trademark Law Amendments Act (P.L. 96-517, December 12, 1980).

[7]The Q3 2019 Global Venture Capital Report, 07 October 2019, https://news.crunchbase.com/news/the-q3-2019-global-venture-capital-report-seed-stage-deals-increase-while-broader-funding-environment-shows-signs-of-erosion.

[8]Synthetic Biology Investment Report 2019 Q2, 17 July 2019, https://synbiobeta.com/wp-content/uploads/2019/07/Synthetic-Biology-Investment-Report-2019Q2-SynBioBeta.pdf.

[9]Title 17 of the U.S. Code—Copyrights.

exchange for meeting regulatory requirements. Regulatory exclusivity is available for drugs, both on- and off-patent (Eisenberg, 2012), but is untested in the biotechnology sector outside of generic and orphan drugs and would likely require new legislation to create or extend to other areas of bioeconomy commercialization.

Investing in the Public Domain

Underpinning much of the U.S. bioeconomy are technologies available in the public domain. In the pre-Bayh–Dole era, most academic scientists did not seek patent protection and instead placed their innovations directly in the public domain through publications and presentations at scientific meetings in accordance with the norms of the academic research community. Like all of these unpatented technologies, many of the technologies developed by academic researchers in the nearly 40 years since the Bayh–Dole Act came into effect are in the public domain, either because researchers have pursued a public domain strategy for the dissemination of their innovations or because the period of patent protection has ended.

The patent system is often associated with exclusivity and monopoly, but in fact is one of the best mechanisms for building the public domain. The quid pro quo of the patent system is to provide a limited period of exclusivity in exchange for disclosure of the innovation to the public. Once the period of exclusivity has expired, the innovation enters the public domain. Examples of foundational biotechnologies that have entered the public domain via the patent system include the recombinant DNA technology developed by Stanley Cohen and Herbert Boyer, the polymerase chain reaction developed by Kary Mullis, and the use of green fluorescent protein for monitoring gene expression developed by Martin Chalfie. Beyond these early patented biotechnologies, it is not uncommon for researchers and others wishing to further develop or use patented technologies to simply await the expiration of the patents. As an example, researchers at the University of Arkansas developed glyphosate-tolerant varieties of soybean after Monsanto's patent on the first generation of Roundup Ready technology expired in March 2015 (Chen et al., 2016). These varieties are available without technology fees, and farmers can save seed for planting in subsequent years. Whereas the dawn of the biotechnology revolution took place in the early 1980s, the U.S. bioeconomy has been benefiting from the era of generic biotechnology, thanks to the patent system, since the early 2000s.

Growth of biotechnology-relevant innovations in the public domain also occurs through the creation of prior art that precludes subsequent patenting. Prior art is information that has been disclosed to the public, before the earliest priority date of a patent application, that would

preclude the granting of a patent for lack of novelty[10] or nonobviousness.[11] Despite ongoing efforts by the U.S. Patent and Trademark Office (USPTO) to improve patent quality,[12] it remains challenging to get the best prior art before patent examiners during the examination process. This is particularly true for prior art published in the nonpatent literature (e.g., scientific journals, conference proceedings).[13] For this reason, those wishing to contribute technology to the public domain may opt to file, and then intentionally abandon, a patent application that provides an enabling disclosure of the technology they wish to contribute. This file-and-abandon strategy replaces the pre-Leahy–Smith America Invents Act procedure known as Statutory Invention Registration[14] that companies typically used to place technology in the public domain as a means of ensuring that their own use of the technology would not be jeopardized by competitor-owned patents.

In building the set of relevant innovations in the public domain, it is important to recognize that patents are not the only type of IP protection that may limit, albeit temporarily, the use of a technology. Material transfer agreements, or MTAs, are commonly used in the life sciences to govern the use of research materials such as plasmids, antibodies, cell lines, and more. Although for most research materials, MTAs need do little more than establish provenance, the high transaction costs of negotiating MTAs and the risk-aversion tendency to include unnecessarily restrictive terms have been well documented (Bubela et al., 2015; Nielsen et al., 2018; Walsh et al., 2005). In the 1990s, NIH developed the Uniform Biological Material Transfer Agreement (UBMTA) and the Simple Letter Agreement, which are now maintained as standards by the Association of University Technology Managers. While these standard MTAs have done much to streamline the MTA negotiation process, they include terms that limit the use and redistribution of materials and hence are not well suited to research materials intended for dissemination within the public domain. Recently, the OpenMTA was introduced as a standard template that would enable provenance tracking and was optimized for dissemination of unpatented materials through the public domain (Kahl et al., 2018). Based on the UBMTA template but with modifications to allow commercial use and redistribution, the OpenMTA has steadily been gaining momentum, with

[10]35 U.S.C. § 102.

[11]35 U.S.C. § 103.

[12]See https://www.uspto.gov/patent/patent-quality.

[13]Colleen V. Chien, Comparative Patent Quality and the Prior Art Gap, guest post 01 October 2019, https://patentlyo.com/patent/2019/10/comparative-patent-quality.html.

[14]35 U.S.C. § 157 (pre-Leahy–Smith America Invents Act) Statutory invention registration.

more than 50 signatories from academic research institutions, biotechnology companies, and community labs.[15]

The public domain is, in essence, a form of property that is owned by, and maintained for the benefit of, the public (Ochoa, 2002). With the continued growth of the U.S. bioeconomy, it will be important to ensure that scientists and engineers and the companies and research institutions that employ them are able to effectively leverage and build on technologies in the public domain. USPTO already provides a number of resources and training opportunities to assist inventors, entrepreneurs, and other stakeholders in better understanding and utilizing the patent system.[16] In addition, nonprofit organizations such as the Public Intellectual Property Resource for Agriculture (Chi-Ham et al., 2012) and Cambia (Jefferson et al., 2018) have made available to the public a number of tools and educational materials to aid in the development of strategies that optimize the creation and use of proprietary and public-domain technologies.

The U.S. Coordinated Framework for Regulation of Biotechnology

Clear regulatory paths for bioeconomy products to enter the market in an efficient, timely, and safe manner help reduce uncertainty for new products and contribute to driving continued innovation within the bioeconomy. The U.S. government regulates many of the products, services, and production processes associated with the bioeconomy because they have the potential to impact public health, safety, welfare, or the environment. In developing the Coordinated Framework for the Regulation of Biotechnology of 1986, the U.S. government focused on characteristics of the product itself, rather than exclusively on the process by which the product was created: "The manufacture by the newer technologies [i.e., genetic engineering] of food, the development of new drugs, medical devices, biologics for humans and animals, and pesticides, will be reviewed by FDA [U.S. Food and Drug Administration], USDA [U.S. Department of Agriculture] and EPA [U.S. Environmental Protection Agency] in essentially the same manner for safety and efficacy as products obtained by other techniques" (OSTP, 1986, p. 23304). U.S. regulations are triggered by the nature of the potential risks to be mitigated—such as those posed by dangerous medical products and devices, impure or adulterated food, or environmental contamination—and not solely because the production process may have employed genetic engineering techniques. Moreover, these regulations do not aspire to eliminate all risk. As stated in the 2017

[15]See https://biobricks.org/openmta.

[16]See https://www.uspto.gov/learning-resources.

Update to the Coordinated Framework, which reaffirmed language in a 1992 update addressing the introduction of biotechnology products into the environment, "oversight is to be applied only where the risk posed by the introduction is unreasonable" (EOP, 2017, p. 4). A 2011 Executive Order further clarifies the interests of the U.S. government in efficient, effective, and innovation-conducive regulation (EOP, 2011).

According to the U.S. government, the current regulatory approach to biotechnology products effectively protects public health and the environment (EOP, 2017). However, the U.S. government also acknowledges that science and technology are moving rapidly, and that it can be difficult to determine which regulatory process is appropriate to which type of product. As a consequence, regulatory agency decision making can under some circumstances be delayed, leading to a perception that the U.S. regulatory system is not agile. For example, from 1988 to 1997, the mean approval time for genetically engineered crops was determined to be 1,321 days, and from 1998 to 2015, the mean approval time was 2,467 days (Smart et al., 2016).

The 2017 Update to the Coordinated Framework clarifies which agencies have responsibility for which types of biotech products (EOP, 2017, p. 1). Three federal agencies, acting under 11 statutes, have primary responsibility for regulating biotechnology products:

- **The U.S. Food and Drug Administration (FDA)** is responsible for the safety and proper labeling of human and animal foods and of cosmetics, and for the safety and efficacy of human and animal drugs and human medical devices. FDA also considers that its animal drug authorities govern the genetic engineering of animals, even apart from its effect on human foods.
- **The U.S. Environmental Protection Agency** is responsible for substances (including products of biotechnology) that have insecticidal, fungicidal, rodenticidal, or other toxic properties. In particular, it exercises broad authority over new chemicals in commerce, which it defines as including certain forms of genetically engineered organisms. This regulatory space has the potential for broad impact on the bioeconomy.[17]

[17]According to the 2017 Update to the Coordinated Framework: "Examples of TSCA [Toxic Substances Control Act] applications include intergeneric microbial biotechnology products for biomass conversion for chemical production; microbial fuel cells; mining and resource extraction; building materials; waste remediation and pollution control; non-pesticidal agriculture applications such as bio-fertilizers; weather and climate modification; various consumer products and all other applications of intergeneric microbial biotechnology products not otherwise excluded under TSCA" (EOP, 2017, p. 13).

- **The U.S. Department of Agriculture (USDA)** is responsible for plant pest and disease risks, noxious weed risks, and the safety and appropriate labeling of certain foods (i.e., meat, poultry, and egg products). USDA regulates plants genetically engineered through the use of bacteria the agency considers to be plant pests, but it does not currently assert the authority to regulate plant biotechnologies, such as genome editing, that do not use such bacteria. However, other authorities, which USDA has not used in the past to regulate biotechnology, might apply.

Table 5-1 summarizes a number of these agencies' statutes and protection goals.

A 2015 White House memorandum from the director of the Office of Science and Technology Policy on "Modernizing the Regulatory System for Biotechnology Products" (OSTP, 2015) calls for a study of "the future landscape of biotechnology products" to identify potential new risks and risk assessment frameworks in order to help regulatory agencies anticipate new types of products that might not be well matched to their existing regulatory processes and risk assessment capabilities. This study was conducted by the National Academies, which in 2017 released the report *Preparing for Future Products of Biotechnology* (*Future Products*) (NASEM, 2017b). The committee that developed the *Future Products* report concluded that the U.S. regulatory system needs to consider many competing interests, including

> supporting innovation, protecting human health, preserving biodiversity, reducing negative environment effects, promoting public confidence in the regulatory process, increasing transparency and predictability in the regulatory process, reducing unnecessary costs and burdens, making use of new tools from a broad array of disciplines, and interacting with the global economy. (NASEM, 2017b, p. 10)

It also concluded that advances in biotechnology over the next 5–10 years threaten to overwhelm the U.S. regulatory system, with regulators facing difficult challenges posed by new types of biotechnology products. Notably, product regulation in the United States includes both ex ante (pre-market testing) and ex post (evaluating performance) components, and regulatory regimes aim to optimize the two, taking benefits and risks into account (Innes, 2004). In 2019, an Executive Order was released that was aimed at capitalizing on benefits from agricultural biotechnology by modernizing regulatory oversight frameworks (White House, 2019).

TABLE 5-1 Statutes and Protection Goals Related to the U.S. Environmental Protection Agency (EPA), the U.S. Food and Drug Administration (FDA), and the U.S. Department of Agriculture (USDA) for the Regulation of Biotechnology Products

Agency	Statute	Protection Goal
EPA	Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA)	Prevent and eliminate unreasonable adverse effects on the environment. • For environmental and occupational risks, this involves comparing economic, social, and environmental risks to human health and the environment and benefits associated with the pesticide use. • For dietary or residential human health effects, the sole standard is the "safety" of all combined exposures to the pesticide and related compounds.
EPA	Federal Food, Drug, and Cosmetic Act	Ensure that no harm will result from aggregate exposure to the pesticide chemical residue, including all anticipated dietary exposures and all other exposures for which there is reliable information.
EPA	Toxic Substances Control Act	Prevent the manufacture, processing, distribution in commerce, use, or disposal of chemical substances, or any combination of such activities with such substances, from presenting an unreasonable risk of injury to health or the environment, including an unreasonable risk to a potentially exposed or susceptible population, without consideration of costs or other nonrisk factors.
FDA	Federal Food, Drug, and Cosmetic Act	Ensure human and animal food is safe, sanitary, and properly labeled. Ensure human and animal drugs are safe and effective. Ensure the reasonable assurance of the safety and effectiveness of devices intended for human use. Ensure cosmetics are safe and properly labeled.
FDA	Public Health Service Act	Ensure the safety, purity, and potency of biological products.
USDA	Animal Health Protection Act	Protect livestock from animal pest and disease risks.

TABLE 5-1 Continued

Agency	Statute	Protection Goal
USDA	Plant Protection Act	Protect agricultural plants and agriculturally important natural resources from damage caused by organisms that pose plant pest or noxious weed risks.
USDA	Federal Meat Inspection Act	Ensure that the United States' commercial supply of meat, poultry, and egg products is safe, wholesome, and correctly labeled.
USDA	Poultry Products Inspection Act	Ensure that the United States' commercial supply of meat, poultry, and egg products is safe, wholesome, and correctly labeled.
USDA	Egg Products Inspection Act	Ensure that the United States' commercial supply of meat, poultry, and egg products is safe, wholesome, and correctly labeled.
USDA	Virus-Serum-Toxin Act	Ensure that veterinary biologics are pure, safe, potent, and effective.

SOURCE: EOP, 2017, p. 9 (table is also Table 3-1 in NASEM, 2017).

The Role of Standards in Supporting Scientific and Technical Progress and Commercialization

Standards-setting activities supported by the U.S. government and by professional communities, including public–private partnerships, can clarify directions of technical progress, weighing the need not to prematurely constrain innovation by setting standards too early with the need to obtain efficiencies and improve interoperability by developing standards and relevant measurement techniques in a timely manner. The U.S. government has generally encouraged the development and use of voluntary consensus standards developed by experts in a field. The National Technology Transfer and Advancement Act of 1995 (P.L. 104-113), for example, asks NIST "to coordinate the use by Federal agencies of private sector standards, emphasizing where possible the use of standards developed by private, consensus organizations," in addition to continuing to carry out NIST's own important standards-setting activities.

A number of different types of open and proprietary standards and reference materials exist across the life sciences and enabling technologies that contribute to the bioeconomy. These include such diverse examples as the NIST monoclonal antibody reference material standard (NIST RM8671), which supports consistent characterization of physicochemical

and biological properties of monoclonal antibodies.[18] As advances in such areas as synthetic biology have continued to drive a number of developments in the bioeconomy, the field has also moved to create a corresponding standards infrastructure. In 2015, the Synthetic Biology Standards Consortium was established as a forum for academic, industry, nonprofit, and public entities to identify metrology needs and technical standards for the community.[19] The development of standards can be particularly challenging in fast-moving fields such as synthetic biology. A report from RAND Europe, commissioned by the British Standards Institute and based on stakeholder interviews, illustrates many perceived benefits of standards in support of innovation and commercialization, while highlighting such challenges as high biological complexity that make effective standardization difficult (Parks et al., 2017).

Targeted Use of Government Purchasing Power and Incentive Programs for Biobased Products

The U.S. government is also a customer of bioeconomy goods and services, using procurement programs and other incentives to stimulate demand and encourage further private investment. One example—USDA's BioPreferred program—is described in Box 5-3. The use of mandates has similarly been credited with providing incentives for industry to develop infrastructure that has advanced biofuel markets in Brazil and the United States (Cicogna et al., 2017).

Procurement by government or public-sector entities accounts for a significant fraction of the demand for goods and services and is increasingly seen as an important factor in achieving innovation policy objectives (Uyarra and Flanagan, 2010). Public procurement is the mechanism by which governments acquire goods and services needed to fulfill their functions. Purchases occur in a number of sectors, including construction, health, custodial, food services, and transportation, as well as in security and defense. Two types of procurement with impact on innovation are "public technology procurement," where a product does not yet exist and there is anticipated demand, and "regular public procurement," where existing products that require no additional R&D are purchased on the basis of available information about price, quantity, and performance. A market "pull," procurement policies can catalyze the creation of new markets and provide certainty for producers.

[18]See https://www.nist.gov/programs-projects/nist-monoclonal-antibody-reference-material-8671.

[19]See https://www.nist.gov/programs-projects/synthetic-biology-standards-consortium-sbsc.

BOX 5-3
The U.S. Department of Agriculture's (USDA's) BioPreferred Program

The 2002 Farm Bill gave rise to the USDA BioPreferred program to increase the development, use, and purchase of biobased products in the United States through two components: a federal procurement requirement for federal agencies and federal contractors and a voluntary certification and labeling program. USDA's BioPreferred biobased products, which are for federal procurements other than food, feed, or fuel, are derived from agricultural and other renewable materials. The BioPreferred program is aimed at reducing U.S. dependence on petroleum and increasing the use of renewable agricultural resources, including agricultural waste.[a] The increased use of agricultural, marine, and forestry materials supports jobs in rural areas as it accelerates the growing bioeconomy.

The growth of the U.S. biobased products industry is readily apparent through analyses of the BioPreferred program. In 2005, USDA designated six product categories for the program; in February 2016, the Secretary of Agriculture announced that USDA had certified more than 2,500 biobased products in 100 product categories.[b] Also in 2016, an economic analysis of the U.S. biobased products industry determined that in 2014, it contributed 4.22 million jobs to the U.S. economy, up from 4.02 million in 2013, and the value added to the U.S. economy was $393 billion, up from $369 billion in 2013 (Golden et al., 2016). Because there is no formal annual reporting requirement for biobased procurement, missing from these achievements is a marked increase in procurement of biobased products over time by federal agencies and contractors.

In March 2015, Executive Order 13693, Planning for Federal Sustainability in the Next Decade, was aimed at maintaining federal leadership in sustainability and reduction of greenhouse gas emissions, promoting innovation, and increasing agencies' efficiency and improving their environmental performance.[c] Acquisition and procurement of sustainable products (e.g., recycled, energy- and water-efficient, biobased) was a key component, and agencies were directed to set annual targets for the number of contracts and annual expenditures so as to achieve at least 95 percent of the BioPreferred procurement requirement. Importantly, annual reporting of such procurements was specified, as was public posting of the information. In January 2017, fiscal year 2017 agency commitments for procurement of sustainable and biobased products were made public by the Office of Management and Budget (OMB, 2017). Executive Order 13693 was revoked on May 17, 2018,[d] and was replaced on the same day by the new Executive Order 13834, Efficient Federal Operations, which lacks reference to sustainable and biobased procurement (EOP, 2018). Given the magnitude of federal procurement and its influence on innovation, this setback in momentum toward measurable biobased procurement by federal agencies and contractors has the potential to hinder the growth of the U.S. bioeconomy.

---

[a] See https://www.biopreferred.gov/BioPreferred/faces/pages/AboutBioPreferred.xhtml.

[b] See https://www.usda.gov/media/press-releases/2016/02/18/fact-sheet-overview-usdas-biopreferred-program.

[c] *Federal Register* 80(57):15871–15884. See https://www.govinfo.gov/content/pkg/FR-2015-03-25/pdf/2015-07016.pdf.

[d] See https://www.fedcenter.gov/programs/eo13693.

The Value of a Skilled Bioeconomy Workforce

As demographics change and the bioeconomy continues to grow in the United States and around the world, a diverse workforce with the skills and training to take advantage of these opportunities will be needed. The United States has a long history of public and private investment in science and technology education and training in areas that will be relevant to future economic growth in the bioeconomy. "Education in science, technology, engineering, and mathematics—STEM—develops, preserves, and disseminates knowledge and skills that convey personal, economic, and social benefits" (NSB and NSF, 2018, p. 12). Higher education, including that offered by community colleges, "provides the advanced work skills needed in an increasingly knowledge-intensive, globally integrated, and innovation-based landscape" (NSB and NSF, 2018, p. 12). In 2018, the federal government released a strategy for STEM education with three aspirational goals: build strong foundations for STEM literacy; increase diversity, equity, and inclusion in STEM; and prepare the STEM workforce for the future (White House, 2018). Similarly, recent reports from the National Academies have looked to the future of graduate and undergraduate education, including in minority-serving institutions, with recommendations to maintain the ability of U.S. educational systems to fully meet the anticipated needs of the 21st century workforce (NASEM, 2018b,c).

Such trends as the convergence of disciplines—biology, chemistry, computing, engineering, and others—to support bioeconomy R&D have led to the creation of new programs to develop the next-generation workforce. Formal training programs in engineering biology and synthetic biology at the undergraduate and graduate levels in the United States continue to evolve rapidly and are multidisciplinary, encompassing elements focused on entrepreneurship, computer training (e.g., Python boot camps), and training in the use of robotics and automation.[20] The long-standing International Genetically Engineered Machine (iGEM) competition has played a valuable role in spurring further interest in synthetic biology, an area driving progress in the bioeconomy. Now 15 years old, the program has engaged more than 30,000 high school and undergraduate students and instructors, with 353 teams from around the world taking part in the 2019 competition. In addition to building scientific skills and interest in engineering biology, iGEM emphasizes responsible conduct of the scientific experiments undertaken by teams and promotes such norms.[21] IGEM awards are given annually for a large range of topics,

[20]See http://diy-bio.com/synthetic-biology-graduate-programs.
[21]See www.igem.org.

including best therapeutic, best diagnostic, best energy, best software, best information processing, and best food and nutrition project, to name just a few. (See Chapter 7 for additional detail on the iGEM competition.)

Also expanding are university biobased product engineering, processing, and product development programs to meet the needs of future industrial biotechnology companies.[22] As developments in the life sciences have become more data-driven, there have also been calls for greater systematic preparation at the undergraduate level to expand data-science talent (NASEM, 2019). Finally, outside of formal academic settings, such efforts as virtual reality exercises have also been proposed to spur interest in bioeconomy-related careers (Hakovirta and Lucia, 2019).

U.S. training and workforce development most closely tied to the bioeconomy have thus far taken place predominantly in synthetic biology and biotechnology, with a few programs focused on bioprocessing.[23] In contrast, a number of European programs are focused specifically on "bioeconomy" training at the master's and Ph.D. levels (Motola et al., 2018), with some recognizing the need for training a specific cadre of economists skilled in the study of primary production, biobased value chains, and societal and economic impacts of bioeconomic developments (Lask et al., 2018). See Chapter 4 for a fuller discussion of a number of metrics in such areas as graduate enrollment and degrees awarded relevant to the U.S. and international bioeconomy workforce.

TRENDS AND CHANGES IN THE BIOECONOMY

Moving forward, the life sciences communities will likely continue to experience change in the form of growing transdisciplinary and team-based science; an increasing shift toward applying engineering approaches to biology; a global environment for science that is driven by sharing, accessing, and analyzing large amounts of data; and changing stakeholders, workforce, and supply chains. These trends will also help shape the future of the U.S. bioeconomy.

Transdisciplinary Integration

Basic research activities have historically been founded around scientific disciplines—areas of knowledge and expertise that have formed the basis for research, as well as for the training and education of the next

[22]See https://www.agmrc.org/directories-state-resources/related-directories/bioprocessing-and-bioproducts-degree-programs.

[23]See https://www.agmrc.org/directories-state-resources/related-directories/bioprocessing-and-bioproducts-degree-programs.

generation of scientists. As the amount of fundamental knowledge about the world has increased in these disciplines, the life science research and educational enterprise has increasingly been focused on convergent or transdisciplinary questions[24] and problems that may require expertise from teams of scientists to make key breakthroughs (see Box 5-4). The disciplines feeding into the bioeconomy also continue to evolve—some are combining in new ways, while some prior fields are coming back because of new developments.

Shift Toward Engineering Approaches

Research in biology has traditionally focused on small-scale, by-hand experimentation aimed at better understanding of biological phenomena. Breakthroughs in technology have enabled a shift to engineering biology for the manufacture of products. Synthetic biology is an example of this shift, with various technologies enabling engineers to "design, build, and test" biological systems (EBRC, 2019; NASEM, 2017b, 2018a). Engineering approaches continue to improve traditional bioeconomy sectors as well, with advances in data science, systems biology "-omics" methods, and automation reducing the amount of trial and error needed to improve biological processes and increasing the scale of production.

Access to and Analysis of Data

Progress in the life sciences and its translation into the bioeconomy are increasingly data-driven. The generation of large amounts of genomic data has become significantly less expensive with the development of high-throughput sequencing, and there is an increasing need to explore approaches to automated curation to assist in managing these growing data streams. However it often remains more expensive to acquire high-value data, particularly well-characterized genotype–phenotype information, than to retain collected data that may one day be of use in addressing new questions. As a result, databases that house and manage this information provide important infrastructure for discovery and innovation. Examples of how the collection, aggregation, and analysis of

[24]Convergence has been defined as "an approach to problem solving that cuts across disciplinary boundaries. It integrates knowledge, tools, and ways of thinking from life and health sciences, physical, mathematical, and computational sciences, engineering disciplines, and beyond to form a comprehensive synthetic framework for tackling scientific and societal challenges that exist at the interfaces of multiple fields. By merging these diverse areas of expertise in a network of partnerships, convergence stimulates innovation from basic science discovery to translational application" (NRC, 2014, p. 1).

BOX 5-4
Convergence of Expertise in Tackling Mosquito-Borne Diseases

Advances in multiple areas may intersect synergistically to create innovation in the bioeconomy. Among the approaches to addressing mosquito-borne diseases being pursued by a number of groups is Project Debug, which exemplifies the convergence of entomology and engineering.[a] This program provides a tool for mosquito abatement based on the release of male *Aedes aegypti* mosquitos infected with the bacterium *Wolbachia*. In this case, *Wolbachia*-infected male mosquitoes are unable to reproduce when they mate with uninfected, wild-type females, reducing the mosquitoes' ability to transmit such diseases as dengue fever, Zika, and others. The effort resulted from a collaboration between the biopesticide start-up company MosquitoMate[b] and Alphabet-backed Verily Life Sciences (Gilbert and Melton, 2018). Engineers at Verily adapted a manual injection-based laboratory infection process to an entirely automated process capable of producing 1.5 million infected male mosquitoes per week. They additionally developed algorithms for controlled release of the infected males and for monitoring of the intended effects on the target mosquito population in "near real time." As of 2019, the team was preparing for another release, but considered the work still to be at an early knowledge-gathering stage. The project has resulted in multiple issued patents (as of June 2019, patents had been granted for separating pupae [US 10251380, US 9992983], conveying eggs [US 10028491], separating or singulating insects [US 10278368, US 10178857], and automating emergence [US 10051845, US 10292375]).

[a]See https://debug.com.
[b]See https://mosquitomate.com.

large genomic and personal health datasets provide new opportunities to advance human health are described below.

Population-Based Identification of New Biotherapeutic Opportunities

Approximately a decade after the turn of the millennium, there emerged a growing consensus that to meet the goals for turning the Human Genome Project into a medically relevant resource, researchers would have to obtain much larger populations than originally anticipated to identify robust genome–phenome associations of the sort that had been anticipated to accelerate medicine (Green and Guyer, 2011). To this end, it was quickly recognized that a national scientific priority would be to accurately clinically characterize these populations and also measure their genomic characteristics affordably (Kohane, 2011). In addition, human health and medicine are rapidly changing with changes in culture and

environment. An example is the current obesity epidemic in many countries and the novel therapies being used to treat its consequences, such as diabetes mellitus. As a result, there is a pressing need to address questions in disease genomics at the population scale and answer them in just a few months rather than decades. Furthermore, in the face of increasing financial pressure on the scientific and health care establishments, these large and timely population studies of unprecedented size now must be performed at much lower cost per subject. Significant cost savings have already been realized in the genomic measurements themselves. "The cost of sequencing DNA dropped by seven orders of magnitude between 2002 and 2008 and has dropped by an additional order of magnitude between 2008 and 2015" (NASEM, 2017b, p. 28). Therefore, the clinical characterization linked to these genomic measurements represents residual and substantial costs.

Cost efficiency in clinical characterization (also termed phenotyping) of a population has been driven by secondary use of clinical annotations that are available in electronic health records (EHRs). Although there is considerable controversy about the clinical value of these systems, the availability of electronic codified data (e.g., diagnoses, procedures, laboratory values, demographics), electronic narrative text (e.g., clinic notes, discharge summaries, radiology summaries), and electronic images (i.e., most radiology studies and a steadily growing minority of pathology tissue histology studies) provides significant data resources. Use of these data for phenotyping populations at scale therefore rests on a multihundred billion dollar infrastructure in the United States alone to support interoperable data sharing associated with EHRs (Halamka and Tripathi, 2017), and also depends on and has accelerated the advanced development of natural language processing and image processing/classification techniques and a multitude of other machine learning methods. The ability to sift through a population with a phenotype of interest represents a substantial advantage, one for which pharmaceutical companies have paid hundreds of millions of dollars. Among these companies was Amgen, which in 2012 paid $415 million for well-characterized patient samples paired to their genetics for only tens of thousands of individuals when it acquired the deCODE project.

Although perhaps not central to the economics of these population analyses but societally just as controversial are the consent regimes under which these population data are gathered. In some instances, patients' consent has been fully obtained for the secondary use of their data (e.g., use of the data for purposes beyond the primary reasons the data were originally collected). In other instances, however, patients' consent has not been fully obtained or documented. Researchers of Deep Mind (a company acquired by Google), for example, were able to access the identified

records of patients in the UK National Health Service (NHS) without the patients' consent or knowledge (Powles and Hodson, 2017). Broader exploration of patient consent regimes and their implications can be found in reports from the Institute of Medicine (IOM, 2003, 2015).

Use of patient data companies The interest in access to well-characterized populations can be better understood through one of several case studies illustrating how finding the right patients for genetic studies can lead to scientific breakthroughs and new medicines that extend or significantly improve the quality of life, as well as substantial return on investment for companies and their shareholders. In 2001, toward the end of the Human Genome Project, an association was found between familial hypercholesterolemia and the gene products of PSCK9. Conversely, several individuals were found to have low levels of "cholesterol" (specifically LDL-C, a lipoprotein that carries cholesterol in blood), a specific subgroup of mutations (also termed genetic variants) in the PSCK9, and a significantly lower incidence of heart disease. It quickly became apparent that this finding provided an opportunity to engineer a "biological" (i.e., intravenously delivered monoclonal antibody) that would reproduce the effect of the genetic variants.

Several large pharmaceutical companies soon were racing to develop and have approved a biological targeting PSCK9. In 2015, Amgen received approval for evolocumab (trade name Repatha) from FDA. Annual sales of the drug are well above $100 million and continue to climb. As with all drug development, being first to market often is a significant financial advantage, and the longer a biological can be marketed while on patent, the larger is the advantage. Indeed, a judge granted Amgen an injunction against large competitors such as Sanofi that had a similar biological obtained through similar insights. Therefore, companies perceive privileged access to populations that can enable insights of this sort to be identified and then translated to a biological as a strategic asset.

Regeneron, for example, entered into a contractual agreement with Geisinger Health Systems that included, among other joint efforts, access to the phenotypic characterization of Geisinger's patient populations (notably, but not only, through processing of Geisinger EHRs). These included specific populations of interest, such as a large group with severe obesity-related diseases, and genetically isolated populations, such as the Amish in Pennsylvania. Included in the agreement was funding for sequencing the exomes[25] initially for 100,000 patients, but now with a target of at least 250,000 (Karow, 2017). The amount invested by Regeneron

[25]The exome encompasses those parts of a genome that contain the regions (or exons) of genes that encode proteins.

in this relationship with Geisinger has not been revealed but has been estimated to be in the hundreds of millions of dollars.

Recently, a flurry of discoveries of associations between specific genetic variants and clinical characteristics have been reported by Geisinger and Regeneron scientists in peer-reviewed scientific publications. Among these associations is that between mutations in the ANGPLT3 gene and decreased risk of cardiovascular disease. This finding led to the discovery of a biological designed to mimic the effect of these mutations (Dewey et al., 2017). Early access to such results is likely to account for the continued enthusiasm for this collaboration on the part of Regeneron's leadership and expansion of the scope of the original agreement.

The UK Biobank: A national example[26] The UK Biobank project provides a contrasting model of harnessing and mining patient populations to advance health care and science. The UK Biobank was established by the Wellcome Trust medical charity, the UK Medical Research Council, the UK Department of Health, and the Scottish and Welsh governments. The project depends on both the preexisting infrastructure of the UK NHS, which itself is a national asset, and in-kind contributions from the NHS. It is focused on 500,000 volunteers in the United Kingdom who, at the time of consent, ranged in age from 40 to 69. Recruitment began in 2006, and characterization and follow-up of these volunteers will continue for 30 years. Among the characterizations of these volunteers are anthropometrics (e.g., height, weight); blood and urine chemistries; clinical assessments, including those abstracted from the volunteers' health records; and for subsets of these patients, imaging studies (e.g., cranial magnetic resonance imaging), genotyping, and whole-exome sequencing. For the latter, a consortium of companies (mostly pharmaceutical) has provided the funding.

From the start, the UK Biobank has been engineered to enable the widest array of researchers to access the data. In March 2012, applications for access were accepted from researchers worldwide, regardless of whether they were in the public or private domain. The only requirements were a research protocol and a nominal fee, along with verification by a UK Biobank committee that the research was in the public interest and related to health. Researchers using the data are encouraged to publish their findings in open-access publications or academic journals and to report all their results back to the UK Biobank. In the 6 years since datasets were opened to researchers, more than 500 studies have been initiated, and hundreds of publications have appeared in the biomedical literature.

U.S. researchers and U.S.-based companies are now using these data from the United Kingdom to identify clinically relevant results. For

[26]See https://www.ukbiobank.ac.uk.

example, a group of investigators from Boston used the UK Biobank's clinical and genotypic data to develop a polygenic risk score that appears to accurately identify those individuals at high risk of coronary artery disease (Khera et al., 2018). Furthermore, many of these investigators are founders of a $191 million–backed company that now seeks to "[expand] our understanding of the natural disease protection provided by genetic modifiers through an integrated approach that *combines studying natural human genetic variation across the globe* and conducting large-scale experiments of gene perturbations" [italics added] (MarketWatch, 2019). These results and business plans rest in large part on one of the largest open-access detailed genomic–phenomic datasets in the world—one that is open to all researchers.

From Sequence to Product: The Contribution of Bioinformatic Databases to Biotech Products

As illustrated above, the collection, aggregation, and analysis of increasingly large amounts of biosciences data has become a key feature of the bioeconomy. Open bioinformatic databases are routinely accessed by basic science researchers, as well as by industry to commercialize products. The first sequences of a human genome, simultaneously published by the for-profit company Celera Genomics and by the public international Human Genome Sequencing Consortium, depended heavily on the use of data generated by the U.S. government–led Human Genome Project (International Human Genome Sequencing Consortium, 2001; Venter et al., 2001). Molecular diagnostics and consumer-facing ancestry tools depend on the identification of single nucleotide polymorphisms (SNPs) as reported in the dbSNP database.[27]

New drugs can now be designed and tested in silico using protein structures derived from the Protein Data Bank.[28] It has been estimated that 210 new molecular entities approved by FDA between 2010 and 2016 can be traced to 5,914 protein structures hosted in that data bank (Westbrook and Burley, 2019). Likewise, DNA synthesis technologies enable researchers to identify new gene functions through computational analysis of GenBank and other databases (Bayer et al., 2009). In addition, an important source of value in many companies rests in proprietary databases.

Both open-source and proprietary bioinformatics software tools, such as those used for genome annotation, depend on open bioinformatics data. In each case, basic research can lead to applications that were

[27]See https://www.ncbi.nlm.nih.gov/snp.
[28]See https://www.wwpdb.org.

unanticipated by the researchers who deposited the original data. Databases such as GenBank also host the patented sequences that result from applied R&D as part of patent disclosure requirements.

While it may be impossible to quantify the total impact of open databases on the bioeconomy, the development of diagnostics, drugs, and synthetic biology products benefits from access to these resources. Mergers and acquisitions in the bioeconomy also provide some insight as to how companies value datasets, and these acquisitions may help identify adjacent technology sectors that have become important to the bioeconomy. For example, Indigo Ag, a company that develops microbial treatments for crops, purchased satellite imaging company TellusLabs in 2018. According to the two companies, this merger brings together datasets that can be leveraged via machine learning to better target products to individual farms.[29]

Contribution of Establishing Standards and Frameworks to the Utility of Life Sciences Datasets

Establishing common standards and frameworks is important to enable taking advantage of data that can advance basic science discovery and innovation. As an example, Box 5-5 describes the value of the Universal Protein Resource for aggregating and analyzing protein sequence and functional information. This example illustrates the essential need for automatic curation capabilities in modern databases, arising from the deluge of incoming data. The value of such databases is not measured by the capability to compile the data automatically, but by the user's ability to have confidence that redundant or erroneous information has been handled.

Despite the value of consolidated scientific databases, the migration of The Arabidopsis Information Resource (TAIR) from a federally funded database to a not-for-profit organization providing access on a subscription basis illustrates a vulnerability of such databases (Berardini et al., 2015). TAIR curated genetic and molecular information on *Arabidopsis*, a model plant widely used in the global scientific community. The database was launched in 1999 and in 2014 reported 178,000 visits per month from 61,000 users worldwide. The mission of the database ecosystem was to provide gold standard functional annotation of the organism to the scientific community, but in 2014, the operators of TAIR reported that its primary mission had been "significantly curtailed" as the result of loss of its main national-level funding. The database was subsequently moved to a not-for-profit organization, and a sustainable subscription model

[29]See https://www.indigoag.com/pages/news/indigo-acquires-telluslabs-to-enhance-agronomic-solutions.

was identified (Reiser et al., 2016). The current TAIR resource operators acknowledge that a transition to subscription-based models is not feasible for all publicly funded databases and propose a range of options to be explored. They furthermore point out that secure funding is necessary for sustainable database operation, but is not the only essential ingredient. Their first recommendation is the development of accurate computationally assisted curation, along with a more comprehensive suite of tools to reduce costs associated with creating and distributing the components of such resources within and to the scientific community. An important general consideration is which organization(s) should fund data preservation and (open) dissemination. Such investments are typically not aligned with the mission of industry; therefore, government support for such infrastructure investments may be justified when considered relative to the cost, in terms of leadership and R&D productivity, of not having such data available.

The Changing Players of Biotechnology Innovation

The formation of companies in the biotech space has changed dramatically in the past decade. While biotech investment has traditionally been focused in the pharmaceutical, agricultural, and industrial biotech sectors, a broader array of application areas and new investors has more recently emerged, including start-ups, that are focused on genetic tool development and services, high-throughput screening technology, textiles, and alternative food proteins (Schmidt, 2019). For example, in 2018 more than $3.8 billion in private capital was raised for 97 companies addressing multiple applications of synthetic biology. In comparison, the fiscal year 2018 NIH budget was more than $27 billion.[30]

Furthermore, many of these companies are not direct products of academic institutions but founded independently or within start-up incubators. Some of these incubators came from the traditional tech sector. An example is Y Combinator—associated with such companies as Airbnb and Dropbox—which has now funded more than 140 biotech companies, with 15 percent of its new companies funded in 2018 being involved in biotech (Rey, 2018).[31] Other incubators—such as IndiBio[32] or QB3[33] (affiliated with the University of California)—have been founded for

[30]See https://www.hhs.gov/about/budget/fy2018/budget-in-brief/nih/index.html.

[31]Ginkgo Bioworks was the first biotechnology company within the Y Combinator incubator. By valuation, it is currently among the top 20 Y Combinator companies (https://www.ycombinator.com/topcompanies), which helps to illustrate the current climate of investor interest in biotechnology.

[32]See https://indiebio.co.

[33]See https://qb3.org.

BOX 5-5
The Universal Protein Resource

The Universal Protein Resource (UniProt) is a product of the UniProt Consortium, a collaboration involving the Protein Information Resource (PIR) in the United States, the European Bioinformatics Institute, and the Swiss Institute of Bioinformatics. The mission of UniProt is to provide the scientific community with a comprehensive, high-quality, and freely accessible resource of protein sequence and functional information.[a] The consortium was launched in 2002 at a time when there was a growing and diverse number of freely accessible databases of information related to proteins, all of which were independently administered and had different underlying schemas and different strengths and weaknesses. These databases included PIR, TrEMBL, and Swiss-Prot (Apweiler et al., 2004) among others, such as those associated with the European Molecular Biology Laboratory, the International Protein Index, the Protein Databank, RefSeq, Flybase, and Wormbase.

This was an exciting time in the life sciences because of the accumulation of genome sequence information for many organisms and the availability of a draft human sequence. The broad life sciences community was building on these foundational data by turning toward the identification and functional characterization of proteins. Scientists looking for information could search each of these resources to compile the available information about any given protein, including references to the underlying peer-reviewed scientific literature. Substantial computational effort, as well as human effort, was dedicated to curating these independent resources, and the same protein might be represented in a number of different databases, possibly with different identifiers and with sometimes conflicting information.

With the launch of UniProt, the three leading protein databases were merged into a single platform that retained the strengths of each. Each protein was assigned a unique identifier. The resulting UniProt "knowledgebase" provided a central database of protein sequences with annotations and functional information. The information from the separate databases was transferred into UniProt in a manner that maintained the "gold standard" of manual curation based on literature and sequence analysis for many entries, augmented by automatic classification and annotation (Apweiler et al., 2004).

the express purpose of launching new biotech companies. Self-funded community labs, such as BioCurious (which started on the crowdfunding platform Kickstarter), have also become de facto preincubators by offering spaces for scientists from both traditional research institutions and nontraditional backgrounds to develop concepts for companies in an open precompetitive space.

The broadening focus and background of companies in the biotech space is resulting in an ecosystem of interdependent companies, analogous to the development and maturation of the digital sector. For example, many companies focus on individual services or product categories, such as biological design and statistical software (e.g., Benchling, Synthace through its Antha software in the United Kingdom, Ryffin) or biology tool components (e.g., Synthego, Caribou). Other companies focus

As of 2019, the UniProt knowledgebase contained nearly 160 million protein sequences, up from about 150,000 in 2004,[a] as well as 54.2 billion data triples (that describe how those entries related to each other).[b] While these measures are remarkable in their own right, it is worth highlighting that even within a single, global platform, a number of redundancies of information had been identified—something that could not have been accomplished without a common platform—and 47 million redundant sequences were removed from the knowledgebase in March 2015. Given the exponential growth in sequences, this "proteome redundancy minimization procedure" (UniProt Consortium, 2017) is estimated to have kept the scale of entries down to 120 million in 2017, compared with an estimated minimum of 361 million sequences if redundant entries had not been removed (UniProt Consortium, 2019).

Moreover, while expert manual curation of data is still a gold standard and continues, UniProt increasingly relies on informatics tools to prioritize articles in the peer-reviewed literature for protein curation. With more than 1 million scientific articles being indexed each year in PubMed, it is impossible for an individual scientist to mine the relevant literature on any given protein. Thus, UniProt saves countless hours of effort by scientists and accelerates the pace of scientific discovery. Indeed, more than 160 other databases used by the community cross-reference UniProt, more than 1.25 million papers have cited the database,[a] and in 2015 the resource had more than 4 million monthly users (UniProt Consortium, 2017). The resource has had broad impacts on the research community. Citation analysis suggests it has impacted research into algorithm development, as well as resource/infrastructure building, in addition to its expected impact on biomedical and biotechnology research, and protein identification, functional annotation, and comparative studies (UniProt Consortium, 2015). UniProt has been financially supported at a level of about $15 million per year since 2002, including support from the National Institutes of Health, European Molecular Biology Laboratory–European Bioinformatics Institute, and the Swiss government.[c]

[a]See www.uniprot.org.
[b]See sparql.uniprot.org.
[c]Cathy Wu, University of Delaware, personal communication, October 17, 2019.

on increasing product yield and addressing scale-up challenges, such as by improving engineering of microbial strains in synthetic biology applications. Still other companies are forming vertically integrated "stacks" or horizontal "platforms" that bundle services together to target specific markets or consolidate work across many markets that all require specific services. An example of such a stack used to advance synthetic biology is shown in Figure 5-2. These tool and service provider companies form a life sciences supply chain that can be globally distributed.

As discussed in further detail in Chapter 3, the changing landscape of biotechnology development and the growing network of service and provider companies pose new challenges for assessing the size and value of the bioeconomy.

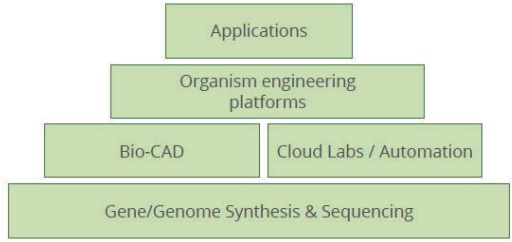


FIGURE 5-2 The synthetic biology "stack." This synthetic biology stack shows several layers that can contribute to a final product. Each horizontal layer represents a set of consolidated tools and services used to expedite the production of a specialized task or product. The products build on one another, as is demonstrated by the fundamental building block of synthetic biology, gene synthesis, and sequencing at the bottom of the stack. The emergence of tools and services that focus on individual portions of the stack represents a specialization of roles that may not be applied to all applications of synthetic biology. For example, while automation is used in many applications of synthetic biology, it is used as an enabling technology, and is not strictly required for successful product development. SOURCE: Cumbers, 2019.

The Changing Bioeconomy Workforce

The rapid pace of research and reliance on enabling technologies and data sharing also pose challenges to how life sciences undergraduate and graduate students are trained, indicating that new approaches to education and training will be needed within universities. In addition, R&D activities are no longer limited to university laboratories. Technology today gives the entire community access to key resources, and science is beginning to be pursued in homes, community centers, online communities, and other nontraditional avenues. Because such simple metrics, such as counting the number of Ph.D.s issued in life sciences subfields, no longer capture all of the R&D efforts relevant to the bioeconomy, updated models for collecting bioeconomy data, including research investments and workforce numbers, will be needed.

As the biotechnology industry continues to grow, classic life sciences training provided at colleges and universities needs to evolve to help prepare students for these types of jobs (Delebecque and Philp, 2019). Students tend to lack interdisciplinary knowledge, and there tends to be a disconnect between what they are taught and what is actual industry practice (Thompson et al., 2018). Industry employees with life sciences knowledge and bachelor's degrees are an important need for a large part of the growing bioeconomy workforce. One study showed that industrial biotechnology companies are overwhelmingly looking to hire entry-level workers with bachelor's degrees (Delebecque and Philp, 2019). While

most employers prefer applicants with a degree in the life sciences, there is greater interest in such qualities as willingness to learn. Some places are leading the way toward training the needed biotechnology workforce. California, for example, mobilized several of its community colleges to prepare a diverse array of students for future careers in the field (Monis, 2018), as illustrated by the Solano Community College Biotechnology and Science Building. This facility contains a simulation of an industrial laboratory where students can obtain hands-on experience in topics related to biomanufacturing. The course load for the college's degree in biomanufacturing is heavily weighted toward science, in addition to courses that help the students simulate biomanufacturing procedures and production (Monis, 2018).

Regional Innovation Hubs and Geographic Distribution of the U.S. Bioeconomy

Regional ecosystems of innovation can arise near areas of major basic research investment, such as public, private, and land-grant universities and federal research laboratories (Baily and Montalbano, 2018; EUA, 2019). These innovation ecosystems, which include start-up companies, small businesses, and affiliated infrastructure, are designed to translate basic research discoveries into economic and societal impact, although the evidence that university entrepreneurship efforts can catalyze regional entrepreneurship vary (Qian and Yao, 2017).

In addition, all regions of the United States make contributions to the bioeconomy. The diversity of contributors to the bioeconomy is reflected in the geographic distribution of relevant facilities across the country. To illustrate, a set of examples focused on a comparison of the distribution of bioethanol fermentation facilities and the distribution of companies focused on biotechnology R&D is presented below. While these examples illustrate geographic distribution within the United States, many of the factors leading to these U.S. distributions can be expected to apply to global efforts to cultivate aspects of the bioeconomy.

Within the United States, fermentation capacity is predominantly for bioethanol production. Total production of bioethanol exceeded 15 billion gallons (approximately 57 billion liters) in 2017, with more than 13 billion of those gallons being produced in the Midwest (see EIA, 2017, Figure 5-3[34]). This capacity is distributed across 200 ethanol plants, 176 of which are located in the Midwest (see EIA, 2019; Figure 5-4). The distribution of bioethanol fermentation plants is driven largely by the distribution of corn production, from which the vast majority of bioethanol is produced.

[34]Midwest as defined by Petroleum Administration for Defense Districts.

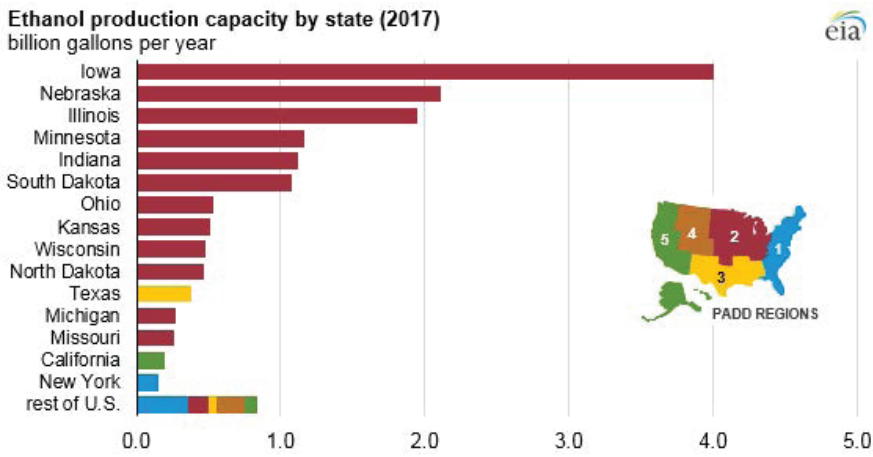


FIGURE 5-3 U.S. ethanol production capacity by state. Significant production of ethanol for fuel is in states from PADD region 2, encompassing the Midwest. NOTE: PADD = Petroleum Administration for Defense Districts classification. SOURCE: EIA, 2017.

In general, the transport of refined higher-value product is preferred to the transport of lower-value feedstocks, leading to fermentation capacity that is generally collocated with feedstock. The optimal locations for growing feedstocks may change as the Earth's climate changes, calling for system designs that are resilient to changes in agricultural land use. If feedstock cultivation moves on a timescale that is faster than the replacement of fermentation capacity, new fermentation capacity may need to be built to follow the feedstocks, new feedstocks may need to be developed to supply existing facilities, or feedstocks will need to be transported.

Corn production in the United States has grown dramatically to supply the bioethanol industry. Over the past 30 years, U.S. corn usage has more than doubled, with the vast majority of that growth going to bioethanol production, and corn usage for feed remaining effectively flat (see Figure 5-5). Currently, approximately 5 billion bushels of corn are converted to about 15 billion gallons of bioethanol. By comparison, about 315 billion gallons of oil (7.5 billion barrels[35]) are used in the United States each year. This relationship between corn and bioethanol output may shift dramatically with the maturation of "second-generation" biofuels that can leverage lignocellulosic biomass rather than the starch from corn as a feedstock. However, expanding fermentation capacity or redirecting some current ethanol fermenters to other bioproducts may be needed to

[35]See https://www.eia.gov/tools/faqs/faq.php.

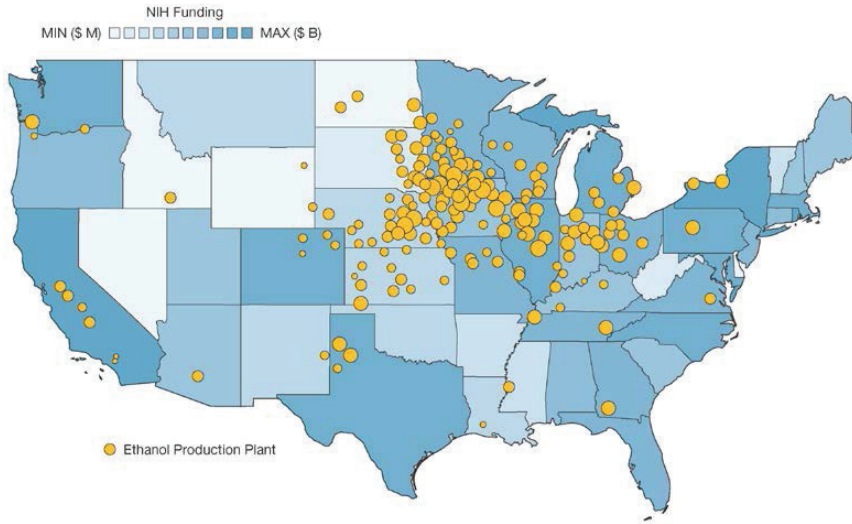


FIGURE 5-4 Distribution of ethanol production plants and National Institutes of Health (NIH) funding. The majority of ethanol production plants (dots) are located in the Midwest, whereas NIH funding for all purposes (shading), which in fiscal year 2018 ranged from approximately $14 million in Wyoming to $4.2 billion in California, tends to go more to the East and West Coasts. NOTE: State NIH funding is not normalized by state population or other potential metrics. SOURCES: Adapted from Distribution of ethanol plants in the United States (https://maps.nrel.gov/transatlas [accessed August 1, 2019]) and NIH awards by location and organization for the 2018 fiscal year (https://report.nih.gov/award/index.cfm [accessed August 1, 2019]).

fully exploit this possibility. A focus on higher-value products may allow dramatic growth in bioproduction without requiring massive increases in feedstock supply.

In contrast to the concentration of fermentation capacity in the Midwest, biotechnology R&D is concentrated largely in coastal states. This trend is observed for NIH research funding, with nearly $10 billion of the $28 billion 2018 NIH budget being awarded to institutions in California, Massachusetts, and New York[36] (see Figure 5-4). This trend is mirrored by venture capital funding, which is overwhelmingly concentrated on the coasts, regardless of sector.[37] Start-ups in both such traditional sectors as biopharmaceuticals and such emerging sectors as synthetic biology have

[36]See https://report.nih.gov/award/index.cfm.

[37]See https://www.nsf.gov/statistics/state-indicators/indicator/venture-capital-deals-per-high-set-establishments.

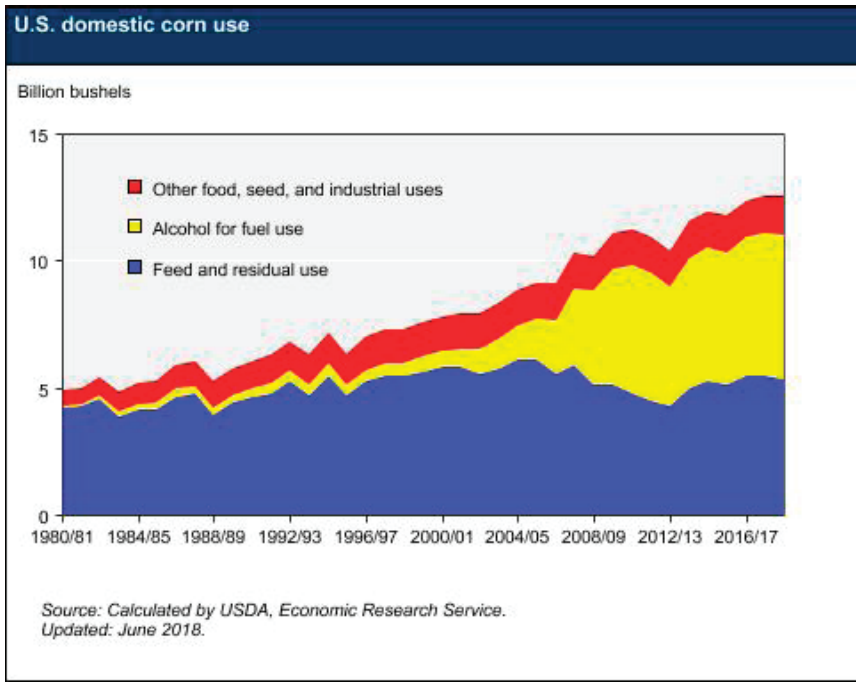


FIGURE 5-5 Corn usage in the United States since the early 2000s. Corn usage for feed, food, industrial uses, and other residual uses has remained relatively flat, while the conversion of corn into alcohol for biofuels has increased. SOURCE: https://www.ers.usda.gov/topics/crops/corn-and-other-feedgrains/feedgrains-sector-at-a-glance (accessed August 1, 2019).

remained concentrated in coastal cities (Synbiobeta, 2018). California, Massachusetts, and New York may have a strong advantage in capturing the future growth of both biotechnology R&D and industry start-ups, as these states provide well-funded research universities, industrial research centers, and access to seed and growth capital. Regional centers with access to similar resources have been successful at growing their biotechnology workforces through focused investment and training programs (Feldman, 2019).

While bioethanol fermentation and biotech R&D represent just two facets of the bioeconomy, they illustrate the complexities of investing in the bioeconomy's growth. For example, growth in the production of bioethanol could be encouraged through lower corn prices, breakthroughs in the utilization of cellulosic biomass, or subsidies for bioethanol-blended gasoline. Yet, those same factors might not stimulate coastal bioeconomic productivity. Similarly, investment in skilled labor to support bioethanol

production would likely favor degrees in chemical engineering rather than molecular biology. To have their intended effect, then, policies intended to safeguard or grow the bioeconomy need to recognize the variability in technologies, workforces, and critical infrastructure. Global competition in the bioeconomy similarly manifests across this spectrum. For example, low-cost sugarcane in Brazil attracts U.S. companies to manufacture there, while government-supported biotech start-up incubators in the United Kingdom vie for U.S.-trained scientists. Regional variation of bioeconomy activities also suggests that different strategies may be most effective based on the region and intended impact. As discussed in this chapter, these strategies include university-driven tech transfer, as well as nonuniversity institutions such as start-up accelerators.

Interdependency and Supply Chains in the Bioeconomy

While large-scale fermentation tends to be closely associated with the regional availability of feedstocks, a resilient supply chain system will be required if growing locations for these feedstocks move in a timeframe that is faster than the replacement of fermentation capacity. In addition, many of the other critical materials of the bioeconomy, such as DNA, cells, and seeds, are mobile and are often developed across borders. A seed designed to be grown in Brazil may have been engineered in the United States using DNA synthesized in Europe with phosphoramidites and other reagents sourced from China. The complexity of these supply chains can result in unforeseen shortages of key materials. For example, more than 80 percent of the world's supply of agar and agarose for biological research derives from the red algae of genus *Gelidium* that are harvested in Morocco; changes in how this harvest is managed have resulted in shortages and price increases (Santos and Melo, 2018). Complex and global supply chains can also be exploited by counterfeiting. Such products as honey are reportedly among the most commonly counterfeited foods through the addition of lower-cost sugars, use of less expensive production processes, rebranding of product origins, and other means (Zhou et al., 2018).

STRATEGIC PLANNING IN SUPPORT OF THE U.S. BIOECONOMY

The pace of advances in the life sciences and converging scientific and technical fields continues to grow through the efforts of diverse stakeholders in public and private organizations in the United States and around the world and supported by multiple funding sources, as well as a growing system of supply and service provider companies. This

complexity makes strategic planning in support of the U.S. bioeconomy highly challenging. Nevertheless, some strategies that may be able to help identify and anticipate trends can be explored. This section illustrates how mapping against TRLs can contribute to further planning.

The TRL scale provides one lens through which the complexity of funding from invention to commercialization has been examined. This scale represents the stages of maturity of a technology, from basic research through the establishment of proof of concept (TRLs 1–3), through additional laboratory testing and prototype validation (TRLs 4–6), to integration in a pilot system and demonstration of readiness for full commercial deployment (TRLs 7–9).

Although it originated in engineering disciplines, the concept of the TRL scale has been adopted, with requisite criterion adaptation, to give funders and policy makers a tool for managing bioscience investments, as illustrated by cases in Europe and the United Kingdom. The European Association of Research and Technology Organisations (EARTO) traced the history of the TRL scale from its origins in NASA and the U.S. Department of Defense, where it was devised to "enable assessment of the maturity of a particular technology and the consistent comparison of maturity between different types of technologies" (EARTO, 2014). EARTO's purpose was to establish TRLs as a policy tool in national funding for the European Union's Horizon 2020 program. As a result, the European Union is now capable of assessing aspects of its bioeconomy efforts in part through a TRL lens (Spatial Foresight et al., 2017). In the European Union, the TRL concept is now being applied to Responsible Research and Innovation via the European Research Area Network Cofund for Biotechnologies (ERA CoBioTech), where evaluation criteria include funding applicants presenting their project outputs in the area of technological and economic development "by describing an envisioned plan to achieve a higher TRL of the processes and technologies."[38,39]

In another example, the UK Engineering and Physical Sciences Research Council has also applied TRLs to its health care investment framework.[40] The concept of TRLs figures explicitly in the definition of the UK National Industrial Biotechnology Strategy for 2030. "The vision

[38]See https://www.cobiotech.eu/lw_resource/datapool/systemfiles/elements/files/85886BE9C7161C71E0539A695E865A64/live/document/ERA_CoBioTech_RRI_Framework.pdf.

[39]Molino and colleagues (2018) have produced a comprehensive analysis of global second-generation biofuel production plant technologies arranged according to TRL.

[40]See https://epsrc.ukri.org/research/ourportfolio/themes/healthcaretechnologies/strategy/toolkit/landscape.

for UK IB is one that transcends politics, where finance is available for business growth and innovation across Technology Readiness Levels."[41]

Within the United States, TRLs are used in national investment strategies. A recent report by the National Academies arrayed broad U.S. programs along a TRL axis (NASEM, 2017a). NSF used TRLs in assessing funding flow into synthetic biology, and the National Institute of Food and Agriculture at USDA has created a TRL for crop research readiness.[42] The interplay of government, industry, and venture funding sources can be illustrated by bioenergy refinery development within the U.S. Department of Energy. Male (2019) documents the investment needed to move from bench-scale biomass conversion (grams per day, investment $1–$5 million) to a full production plant (>250 tonnes per day biomass, investment $250–$500 million).

TRLs serve as a convenient *x*-axis for examining the so-called "valley of death" for movement from invention to commercialization. The Global Federation of Competitiveness Councils uses this format to illustrate the gap between earlier technology developers in the public sector and later commercial producers in the private sector (see Figure 5-6). The gap is due to the inability to fund derisking activities, including prototype development and the collection of data necessary for manufacturing scale-up.

The NSF Engineering Research Centers program has elaborated aspects of a policy funding strategy for Engineering Research Centers to address this gap (Jackson, 2011). Jackson likens the innovation ecosystem to biological ecosystems observed in nature. One concept relevant to the design–build–test cycle is the role of rapid-prototyping infrastructure. Jackson argues that a "bridge" across the valley of death can be created by infrastructure investments that enable rapid prototyping. Such investments lower costs to start-ups for engaging in innovation and raise the success rate of innovation toward a commercially relevant target.

CONCLUSIONS

This chapter described the system for translating research into innovation in the U.S. bioeconomy; trends in the pace, nature, and scope of developments that support life sciences innovation; and a number of areas in which federal and private-sector policies and practices support and sustain U.S. leadership in the bioeconomy. Based on the findings

[41]See http://beaconwales.org/uploads/resources/UK_Industrial_Strategy_to_2030.pdf.

[42]See https://nifa.usda.gov/sites/default/files/resources/Crop%20Research%20Technology%20Readiness%20Level%202018.docx.

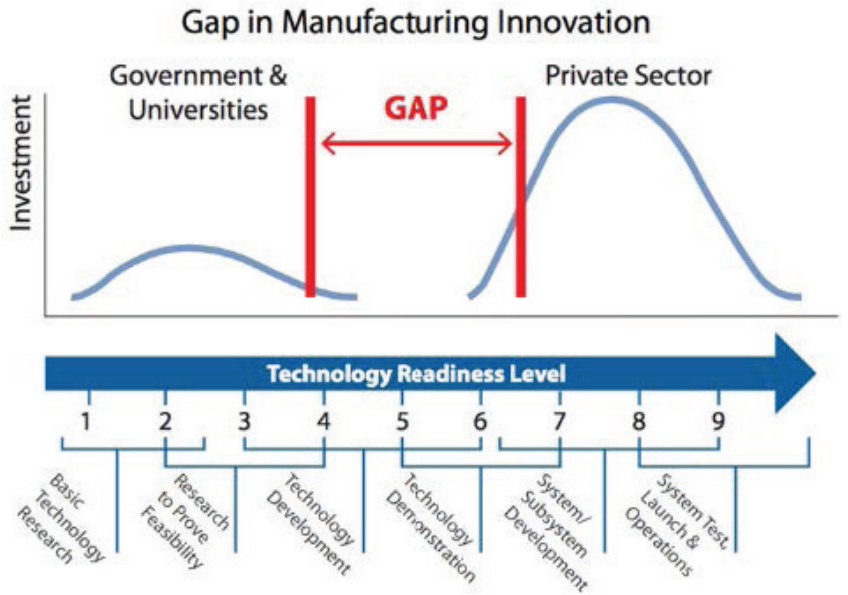


FIGURE 5-6 Mapping research generally undertaken or supported by the federal government and universities along a TRL axis. These entities fund primarily TRLs 1–4, basic research to proof of feasibility. Efforts supported or undertaken by the private sector tend to reside in TRLs 6–9, systems development, testing, launch, and operations. Technology development and demonstration occur in TRLs 3–7, and these overlap with late stages of proof of feasibility (government and university funded) and early stages of systems development (private-sector funded). This represents the "valley of death," characterized by critical steps to transition an idea out of the laboratory and into commercial development, but likewise occurring in a gap of ambiguous funding source. SOURCE: Wince-Smith, 2017.

documented in this discussion, the committee arrived at several conclusions related to discovery and innovation in the bioeconomy.

Conclusion 5-1: Maintaining U.S. bioeconomy leadership will require sustaining a vibrant science and technology base in relevant areas, an ecosystem that encompasses start-up companies as well as large-scale manufacturing, skilled human resources, an agile and effective regulatory system, and other policies that support innovation and commercialization of the research and entrepreneurial enterprise.

A number of trends are driving discovery and economic impact in the bioeconomy, including increasingly convergent/transdisciplinary science;

a shift toward applying engineering approaches to biological problems; access to large biological datasets and the tools needed to analyze such data; and new opportunities to translate research to innovation in start-up incubators, community labs, and other venues that complement traditional university- and national laboratory-based research.

Conclusion 5-2: The continued discovery of new and exciting biology and the continued creation of enabling platform technologies and shifts in how researchers and developers approach problems that require transdisciplinary integration are needed to sustain the creation of new application areas in the bioeconomy and to accelerate the timelines for commercial translation.

Conclusion 5-3: Strategies that enhance access to data repositories and to software and other tools for data analysis, along with creation of data standards frameworks, would increase the ability of U.S. researchers and developers to create bioeconomy opportunities. The impact of expanded access to these resources is challenging to quantify, but a sense of their potential value can be extrapolated from investments in data being made by private-sector companies.

As the United States continues to grow and sustain its bioeconomy ecosystem, it is important to recognize that all stakeholders are involved in these efforts that it will be important to integrate their input. To assist policy makers and stakeholders in the bioeconomy, the committee notes the following.

Conclusion 5-4: No one entity within the U.S. government or among nonfederal stakeholders is responsible for the bioeconomy. This reality creates a gap in the ability of policy makers to anticipate trends and develop coherent policies to support continued U.S. growth and leadership in the bioeconomy. However, the expanded use of such planning tools as Technology Readiness Levels, biobased procurement programs, and other strategies would provide opportunities to support and grow the bioeconomy across all regions of the United States, enabling bioeconomy development to contribute to both urban and rural prosperity.

This chapter of the report has explored how best to sustain the ecosystem of stakeholders within the bioeconomy. The next chapter shifts the discussion to additional strategies for looking to the future to anticipate trends and changes through horizon scanning processes that can help support improved strategic planning.

REFERENCES

Apweiler, R., A. Bairoch, C. H. Wu, W. C. Barker, B. Boeckmann, S. Ferro, E. Gasteiger, H. Huang, R. Lopez, M. Magrane, M. J. Martin, D. A. Natale, C. O'Donovan, N. Redaschi, and L. S. L. Yeh. 2004. UniProt: The Universal Protein Knowledgebase. *Nucleic Acids Research* 32:D115–D119.

Baily, M. N., and N. Montalbano. 2018. *Clusters and innovation districts: Lessons from the United States Experience*. Washington, DC: Brookings Institution. https://www.brookings.edu/wp-content/uploads/2018/01/es_20180116_bailyclustersandinnovation.pdf (accessed September 3, 2019).

Bayer, T. S., D. M. Widmaier, K. Temme, E. A. Mirsky, D. V. Santi, and C. A. Voigt. 2009. Synthesis of methyl halides from biomass using engineered microbes. *Journal of the American Chemical Society* 131(18):6508–6515. doi: 10.1021/ja809461u.

Berardini, T. Z., L. Reiser, D. Li, Y. Mezheritsky, R. Muller, E. Strait, and E. Huala. 2015. The Arabidopsis Information Resource: Making and mining the "gold standard" annotated reference plant genome. *Genesis* 53:474–485. https://www.arabidopsis.org/about/Berardini_et_al-2015-genesis.pdf (accessed September 3, 2019).

Bristow, M. R., L. A. Leinwand, and E. N. Olson. 2018. Entrepreneurialism in the translational biologic sciences: Why, how, and however. *JACC: Basic to Translational Science* 3(1):1–8.

Bubela, T., J. Guebert, and A. Mishra. 2015. Use and misuse of material transfer agreements: Lessons in proportionality from research, repositories, and litigation. *PLoS Biology* 13:e1002060.

Burk, D. L. 2018. DNA copyright in the administrative state. *UC Davis Law Review* 51:1297–1349.

Bush, V. 1945. *Science, the endless frontier: A report to the President*. https://www.nsf.gov/od/lpa/nsf50/vbush1945.htm (accessed September 3, 2019).

Carrico, J. A., M. Rossi, J. Moran-Gillad, G. Van Domselaar, and M. Ramirez. 2019. A primer on microbial bioinformatics for nonbioinformaticians. *Clinical Microbiology and Infection* 24(4):342–349.

Chen, P., R. Bacon, T. Hart, M. Orazaly, L. Florez-Palacios, P. Manjarrez-Sandoval, C. Wu, D. Rogers, G. Bathke, D. Ahrent-Wisdom, R. Sherman, and S. Clark. 2016. Purification and production of breeder seed and foundation seed of University of Arkansas System Division of Agriculture soybean lines. In *Arkansas Soybean Research Studies*, edited by J. Ross. Arkansas Agricultural Experiment Station. https://arkansas-ag-news.uark.edu/pdf/648_Arkansas_Soybean_Research_Studies_2016.pdf (accessed October 14, 2019).

Chi-Ham, C. L., S. Boettiger, R. Figueroa-Balderas, S. Bird, J. N. Geoola, P. Zamora, M. Alandete-Saez, and A. B. Bennett. 2012. An intellectual property sharing initiative in agricultural biotechnology: Development of broadly accessible technologies for plant transformation. *Plant Biotechnology Journal* 10(5):501–510.

Cicogna, M. P. V., M. Khanna, and D. Zilberman. 2017. Prospects for biofuel production in Brazil: Role of market and policy uncertainties. In *Handbook of bioenergy economics and policy*, Vol. II. New York: Springer International Publishing. Pp. 89–117.

Courneya, J. P., and A. Mayo. 2018. High-performance computing service for bioinformatics and data science. *Journal of the Medical Library Association* 106(4):494–495.

Cumbers, J. 2019. *Defining the bioeconomy*. Presentation to the Committee on Safeguarding the Bioeconomy, January 28. http://nas-sites.org/dels/studies/bioeconomy/meeting-1 (accessed October 30, 2019).

Delebecque, C. J., and J. Philp. 2019. Education and training for industrial biotechnology and engineering biology. *Engineering Biology* 3(1). doi: 10.1049/enb.2018.0001.

Dewey, F. E., V. Gusarova, R. L. Dunbar, C. O'Dushlaine, C. Schurmann, O. Gottesman, et al. 2017. Genetic and pharmacologic inactivation of ANGPTL3 and cardiovascular disease. *New England Journal of Medicine* 377:211–221. doi: 10.1056/NEJMoa1612790.

Dolgin, E. 2019. Massive NIH–industry project opens portals to target validation. *Nature Reviews Drug Discovery*, February 27. https://www.nature.com/articles/d41573-019-00033-8 (accessed September 3, 2019).

EARTO (European Association of Research and Technology Organisations). 2014. *The TRL scale as a research & innovation policy tool, EARTO recommendations*. https://www.earto.eu/wp-content/uploads/The_TRL_Scale_as_a_R_I_Policy_Tool_-_EARTO_Recommendations_-_Final.pdf (accessed October 3, 2019).

EBRC (Engineering Biology Research Consortium). 2019. *Engineering biology: A research roadmap for the next-generation bioeconomy*. https://roadmap.ebrc.org (accessed September 3, 2019).

EIA (U.S. Energy Information Administration). 2017. *U.S. ethanol production capacity continues to increase*. https://www.eia.gov/todayinenergy/detail.php?id=31832 (accessed September 3, 2019).

EIA. 2019. *U.S. fuel ethanol plant production capacity*. https://www.eia.gov/petroleum/ethanolcapacity/index.php (accessed September 3, 2019).

Eisenberg, R. S. 2012. Patents and regulatory exclusivity. In *The Oxford Handbook of the Economics of the Biopharmaceutical Industry*, edited by P. Danzon and S. Nicholson. Oxford, UK: Oxford University Press. Pp. 167–198. https://repository.law.umich.edu/book_chapters/126 (accessed October 14, 2019).

EOP (Executive Office of the President). 2011. *Improving regulation and regulatory review*. Executive Order 13563, January 18, 2011. https://obamawhitehouse.archives.gov/the-press-office/2011/01/18/executive-order-13563-improving-regulation-and-regulatory-review (accessed October 1, 2019).

EOP. 2017. *Modernizing the regulatory system for biotechnology products: Final version of the 2017 update to the coordinated framework for the regulation of biotechnology*. https://obamawhitehouse.archives.gov/sites/default/files/microsites/ostp/2017_coordinated_framework_update.pdf (accessed October 3, 2019).

EOP. 2018. *Efficient federal operations.* Executive Order 13834. *Federal Register* 83:23771–23774 https://www.federalregister.gov/documents/2018/05/22/2018-11101/efficient-federal-operations (accessed October 18, 2019).

EUA (European University Association). 2019. *The role of universities in regional innovation ecosystems*. https://eua.eu/downloads/publications/eua%20innovation%20ecosystem%20report%202019v1.1_final_digital.pdf (accessed September 3, 2019).

Feldman, M. 2019. *The economics of innovation and the commercialization of research*. Presentation to the Committee on Safeguarding the Bioeconomy, May 1. http://nas-sites.org/dels/studies/bioeconomy/meeting-3 (accessed October 14. 2019).

Gilbert, J. A., and L. Melton. 2018. Verily project releases millions of factory-reared mosquitoes. *Nature Biotechnology* 36:781–782.

Golden, J. S., R. B. Handfield, J. Daystar, and T. E. McConnell. 2016. *An economic impact analysis of the U.S. biobased products industry.* U.S. Department of Agriculture. https://www.biopreferred.gov/BPResources/file/BiobasedProductsEconomicAnalysis2016.pdf.

Green, E. D., and M. S. Guyer. 2011. National Human Genome Research Institute. Charting a course for genomic medicine from base pairs to bedside. *Nature* 470:204–213. doi: 10.1038/nature09764.

Hakovirta, M., and L. Lucia. 2019. Informal STEM education will accelerate the bioeconomy. *Nature Biotechnology* 37:103–104. https://www.nature.com/articles/nbt.4331 (accessed September 3, 2019).

Halamka, J. D., and M. Tripathi. 2017. The HITECH era in retrospect. *New England Journal of Medicine* 377:907–909. doi: 10.1056/NEJMp1709851.

Hockberger, P., J. Weiss, A. Rosen, and A. Ott. 2018. Building a sustainable portfolio of core facilities: A case study. *Journal of Biomolecular Techniques* 29(3):79–92.

Holman, C. M. 2017. Charting the contours of a copyright regime optimized for engineered genetic code. *Oklahoma Law Review* 69(3). http://digitalcommons.law.ou.edu/olr/vol69/iss3/2 (accessed October 14, 2019).

IAC (InterAcademy Council). 2014. *Inventing a better future: A strategy for building worldwide capacities in science and technology*. Amsterdam, The Netherlands: InterAcademy Council. http://www.interacademies.org/33347.aspx?id=33347 (accessed October 3, 2019).

Innes, R. 2004. Enforcement costs, optimal sanctions, and the choice between ex-post liability and ex-ante regulation. *International Review of Law and Economics* 24:29–48.

International Human Genome Sequencing Consortium. 2001. Initial sequencing and analysis of the human genome. *Nature* 409(6822):860–921.

IOM (Institute of Medicine). 2003. *Responsible research: A systems approach to protecting research participants*. Washington, DC: The National Academies Press. https://doi.org/10.17226/10508.

IOM. 2015. *Informed consent and health literacy: Workshop summary*. Washington, DC: The National Academies Press. https://doi.org/10.17226/19019.

Jackson, D. 2011. What is an innovation ecosystem? National Science Foundation. http://erc-assoc.org/sites/default/files/topics/policy_studies/DJackson_Innovation%20Ecosystem_03-15-11.pdf.

Jefferson, O. A., A. Jaffe, D. Ashton, B. Warren, D. Koellhofer, U. Dulleck, A. Ballagh, J. Moe, M. DiCuccio, K. Ward, G. Bilder, K. Dolby, and R. A Jefferson. 2018. Mapping the global influence of published research on industry and innovation. *Nature Biotechnology* 36:31–39.

Kahl, L., J. Molloy, N. Patron, C. Matthewman, J. Haseloff, D. Grewal, R. Johnson, and D. Endy. 2018. Opening options for material transfer. *Nature Biotechnology* 36(10):923–927.

Karow, J. 2017. Geisinger experience implementing precision medicine spurs new effort to help others do the same. *GenomeWeb*, November 16. https://www.genomeweb.com/molecular-diagnostics/geisinger-experience-implementing-precision-medicine-spurs-new-effort-help (accessed September 3, 2019).

Khera, A. V., M. Chaffin, K. G. Aragam, M. E. Haas, C. Roselli, S. H. Choi, P. Natarajan, E. S. Lander, S. A. Lubitz, P. T. Ellinor, and S. Kathiresan. 2018. Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations. *Nature Genetics* 50:1219–1224. doi: 10.1038/s41588-018-0183-z.

Kohane, I. S. 2011. Using electronic health records to drive discovery in disease genomics. *Nature Reviews Genetics* 12(6):417–428. doi: 10.1038/nrg2999.

Lask, J., J. Maier, B. Tchouga, and R. Vargas-Carpintero. 2018. The bioeconomist. In *Bioeconomy: Shaping the transition to a sustainable, biobased economy*, edited by I. Lewandowski. Cham, Switzerland: Springer. Pp 343–356. doi: 10.1007/978-3-319-68152-8.

Link, A. N., and L. T. R. Morrison. 2019. The U.S. small business innovation research program. In *Innovative activity in minority-owned and women-owned business: Evidence from the U.S. Small Business Innovation Research Program*. Cham, Switzerland: Springer. Pp. 13–27. doi: 10.1007/978-3-030-21534-7.

Male, J. 2019. BETO overview, slide 18. 2019 Project Peer Review, March 4. https://www.energy.gov/sites/prod/files/2019/03/f60/Day%201_Plenary_Male_BETO_Overview.pdf (accessed October 14, 2019).

MarketWatch. 2019. *Maze Therapeutics launches with $191 million to focus on translating genetic insights into new medicines*. https://www.marketwatch.com/press-release/maze-therapeutics-launches-with-191-million-to-focus-on-translating-genetic-insights-into-new-medicines-2019-02-28 (accessed September 3, 2019).

Molino, A., V. Larocca, S. Chianese, and D. Musmarra. 2018. Biofuels production by biomass gasification: A review. *Energies* 11(4):811. doi: 10.3390/en11040811.

Monis, I. 2018. Designing for STEM: California community colleges are helping shape the STEM workforce of the future. *Planning for Higher Education Journal* 47(1):32–38.

Motola, V., I. De Bari, N. Pierro, and A. Giocoli (ENEA). 2018. *Bioeconomy and biorefining strategies in the EU member states and beyond*. IEA bioenergy task 42. https://www.ieabioenergy.com/wp-content/uploads/2018/12/Bioeconomy-and-Biorefining-Strategies_Final-Report_DEC2018.pdf (accessed October 30, 2019).

Narayanan, D., and M. Weingarten. 2018. Chapter 9—An introduction to the National Institutes of Health SBIR/STTR programs. In *Medical innovation: Concept to commercialization*, edited by K. E. Behrns, B. Gingles, and M. G. Sarr. Cambridge, MA: Academic Press. Pp. 87–100.

NASEM (National Academies of Sciences, Engineering, and Medicine). 2017a. *A new vision for center-based engineering research*. Washington, DC: The National Academies Press. https://doi.org/10.17226/24767.

NASEM. 2017b. *Preparing for future products of biotechnology*. Washington, DC: The National Academies Press. https://doi.org/10.17226/24605.

NASEM. 2018a. *Biodefense in the age of synthetic biology*. Washington, DC: The National Academies Press. https://doi.org/10.17226/24890.

NASEM. 2018b. *Data science for undergraduates: Opportunities and options*. Washington, DC: The National Academies Press. https://doi.org/10.17226/25104.

NASEM. 2018c. *Graduate STEM education for the 21st century*. Washington, DC: The National Academies Press. https://doi.org/10.17226/25038.

NASEM. 2018d. *Open science by design: Realizing a vision for 21st century research*. Washington, DC: The National Academies Press. https://doi.org/10.17226/25116.

NASEM. 2019. *Minority serving institutions: America's underutilized resource for strengthening the STEM workforce*. Washington, DC: The National Academies Press. https://doi.org/10.17226/25257.

Nature Biotechnology [Editorial]. 2014. The service-based bioeconomy. 32:597. https://www.nature.com/articles/nbt.2961 (accessed October 14, 2019).

Nielsen, J., T. Bubela, D. R. C. Chalmers, A. Johns, L. Kahl, J. Kamens, C. Lawson, J. Liddicoat, R. McWhirter, A. Monotti, J. Scheibner, T. Whitton, and D. Nicol. 2018. Provenance and risk in transfer of biological materials. *PLoS Biology* 16(8):e2006031.

NIST (National Institute of Standards and Technology). 2019. *Return on investment initiative for unleashing American innovation*. NIST Special Publication 1234. https://nvlpubs.nist.gov/nistpubs/SpecialPublications/NIST.SP.1234.pdf (accessed October 14, 2019).

NRC (National Research Council). 1992. *Responsible science, Volume I: Ensuring the integrity of the research process*. Washington, DC: National Academy Press.

NRC. 2004. *A patent system for the 21st century*. Washington, DC: The National Academies Press. https://doi.org/10.17226/10976.

NRC. 2011. *Managing university intellectual property in the public interest*. Washington, DC: The National Academies Press. https://doi.org/10.17226/13001.

NRC. 2014. *Convergence: Facilitating transdisciplinary integration of life sciences, physical sciences, engineering, and beyond*. Washington, DC: The National Academies Press. https://doi.org/10.17226/18722.

NSB and NSF (National Science Board and National Science Foundation). 2018. *2018 science & engineering indicators—Digest*. https://www.nsf.gov/statistics/2018/nsb20181/assets/1407/digest.pdf (accessed October 8, 2019).

Ochoa, T. T. 2002. Origins and meanings of the public domain. *University of Dayton Law Review* 28:215. https://digitalcommons.law.scu.edu/facpubs/80 (accessed October 14, 2019).

OECD (Organisation for Economic Co-operation and Development)/Eurostat. 2018. *Oslo manual 2018: Guidelines for collecting, reporting and using data on innovation*, 4th edition. Paris, France: OECD Publishing. doi: 10.1787/9789264304604-en.

OMB (Office of Management and Budget). 2017. *Report to Congress on Implementation of Section 6002 of the Resource Conservation and Recovery Act (RCRA); Section 9002 of the Farm Security and Rural Investment Act of 2002; and Section 9002 of the Agricultural Act of 2014.* https://www.whitehouse.gov/sites/whitehouse.gov/files/omb/procurement/reports/2017_rcra_report.pdf (accessed October 14, 2019).

OSTP (Office of Science and Technology Policy). 1986. Coordinated framework for regulation of biotechnology; announcement of policy and notice for public comment. *Federal Register* 51(123):23302–23309. https://ww.govinfo.gov/content/pkg/FR-1986-06-26/pdf/FR-1986-06-26.pdf.

OSTP. 2015. *Modernizing the regulatory system for biotechnology products*. Memorandum for Heads of Food and Drug Administration, Environmental Protection Agency, and Department of Agriculture, July 2. https://www.epa.gov/sites/production/files/2016-12/documents/modernizing_the_reg_system_for_biotech_products_memo_final.pdf (accessed October 30, 2019).

Parks, S., I. Ghiga, L. Lepetit, S. Parris, J. Chataway, and M. Morgan Jones. 2017. *Developing standards to support the synthetic biology value chain*. Santa Monica, CA: RAND Corporation. doi: 10.7249/RR1527.

Powles, J., and H. Hodson. 2017. Google DeepMind and healthcare in an age of algorithms. *Health and Technology* 7(4):351–367. doi: 10.1007/s12553-017-0179-1.

Qian, H., and X. Yao. 2017. *The role of research universities in U.S. college-town entrepreneurial ecosystems*. doi: 10.13140/RG.2.2.12370.15043.

Reiser, L., T. Z. Berardini, D. Li, R. Muller, E. M. Strait, Q. Li, Y. Mezheritsky, A. Vetushko, and E. Huala. 2016. Sustainable funding for biocuration: The Arabidopsis Information Resource (TAIR) as a case study of a subscription-based funding model. *Database: The Journal of Biological Databases and Curation* baw018. doi: 10.1093/database/baw018.

Rey, D. 2018. There are now 141 bio companies funded by YC. *Y Combinator*, September 11. https://blog.ycombinator.com/there-are-now-141-bio-companies-funded-by-yc (accessed September 3, 2019).

Santos, R., and R. A. Melo. 2018. Global shortage of technical agars: Back to basics (resource management). *Journal of Applied Phycology* 30(4):2463–2473. https://link.springer.com/article/10.1007/s10811-018-1425-2 (accessed September 3, 2019).

Schmidt, C. 2019. Meet the 25 synthetic biology companies that raised $652M this quarter. *Synbiobeta*, April 10. https://synbiobeta.com/meet-the-25-synthetic-biology-companies-that-raised-652m-this-quarter (accessed September 3, 2019).

Sherkow, J. S. 2016. Protecting products versus platforms. *Nature Biotechnology* 34:462–465.

Smart, R. D., M. Blum, and J. Wessler. 2016. Trends in approval times for genetically engineered crops in the United States and the European Union. *Journal of Agricultural Economics* 68:182–198. https://onlinelibrary.wiley.com/doi/abs/10.1111/1477-9552.12171 (accessed October 18, 2019).

Spatial Foresight, SWECO, ÖIR, t33, Nordregio, Berman Group, and Infyde. 2017. *Bioeconomy development in EU regions. Mapping of EU member states'/regions' research and innovation plans & strategies for smart specialisation (RIS3) on bioeconomy for 2014–2020*. DG Research & Innovation, European Commission, Brussels. https://ec.europa.eu/research/bioeconomy/pdf/publications/bioeconomy_development_in_eu_regions.pdf (accessed October 3, 2019).

Stephens, Z. D., S. Y. Lee, F. Faghri, R. H. Campbell, C. Zhai, M. J. Efron, R. Iyer, M. C. Schatz, S. Sinha, and G. E. Robinson. 2015. Big data: Astronomical or genomical? *PLoS Biology* 13(7):e1002195.

Synbiobeta. 2018. *Synthetic biology annual investment report*. https://synbiobeta.com/reports/investment-report-2018 (accessed September 3, 2019).

Thompson, C., J. Sanchez, M. Smith, J. Costello, A. Madabushi, N. Schuh-Nuhfer, R. Miranda, B. Gaines, K. Kennedy, M. Tangrea, and D. Rivers. 2018. Improving undergraduate life science education for the biosciences workforce: Overcoming the disconnect between educators and industry. *CBE—Life Sciences Education* 17(3). https://www.lifescied.org/doi/full/10.1187/cbe.18-03-0047?url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Across ref.org&rfr_dat=cr_pub%3Dpubmed& (accessed October 18, 2019).

Torrance, A. W., and L. Kahl. 2014. Bringing standards to life: Synthetic biology standards and intellectual property. *Santa Clara High Technology Law Journal* 30(2). https://ssrn.com/abstract=2426235 (accessed October 14, 2019).

UniProt Consortium. 2015. UniProt: A hub for protein information. *Nucleic Acids Research* 43:D204–D212.

UniProt Consortium. 2017. UniProt: The Universal Protein Knowledgebase. *Nucleic Acids Research* 45:D158–D169.

UniProt Consortium. 2019. UniProt: A worldwide hub of protein knowledge. *Nucleic Acids Research* 47:D506–D515.

Uyarra, E., and K. Flanagan. 2010. Understanding the innovation impacts of public procurement. *European Planning Studies* 18(Issue 1). doi: 10.1080/09654310903343567.

Venter, J. C., M. D. Adams, E. W. Myers, P. W. Li, R. J. Mural1, G. G. Sutton, H. O. Smith, M. Yandell, C. A. Evans, R. Holt, et al. 2001. The sequence of the human genome. *Science* 291(5507):1304–1351.

Walsh, J. P., C. Cho, and W. M. Cohen. 2005. View from the bench: Patents and material transfers. *Science* 309(5743):2002–2003.

WEF (World Economic Forum). 2018. *The Global Competitiveness Report 2018*. http://reports.weforum.org/global-competitiveness-report-2018 (accessed October 18, 2019).

Westbrook, J. D., and S. K. Burley. 2019. How structural biologists and the protein data bank contributed to recent FDA new drug approvals. *Perspective* 27(2):211–217. doi: 10.1016/j.str.2018.11.007.

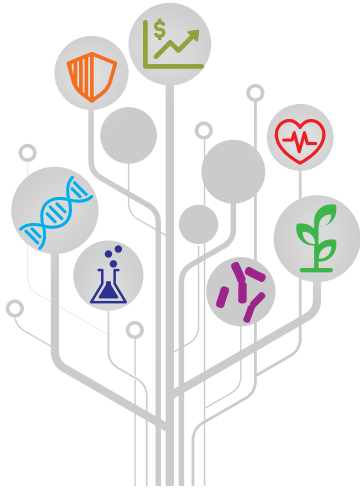
White House. 2012. *The National Bioeconomy Blueprint*. https://obamawhitehouse.archives.gov/sites/default/files/microsites/ostp/national_bioeconomy_blueprint_april_2012.pdf (accessed September 3, 2019).

White House. 2018. *The U.S. STEM strategy*. https://www.whitehouse.gov/wp-content/uploads/2018/12/STEM-Education-Strategic-Plan-2018.pdf (accessed September 3, 2019).

White House. 2019. *Executive order on modernizing the regulatory framework for agricultural biotechnology products.* https://www.whitehouse.gov/presidential-actions/executive-order-modernizing-regulatory-framework-agricultural-biotechnology-products (accessed September 3, 2019).

Wince-Smith, D. 2017. Universities are wellsprings of innovation, drivers of regional economies. *Medium*, February 14. https://blog.thegfcc.org/universities-are-wellsprings-of-innovation-drivers-of-regional-economies-8a3c097e6cc (accessed September 3, 2019).

Zhou, X., M. P. Taylor, H. Salouros, and S. Prasad. 2018. Authenticity and geographic origin of global honeys determined using carbon isotope ratios and trace elements. *Scientific Reports* 8. https://www.nature.com/articles/s41598-018-32764-w (accessed August 1, 2019).



6 HORIZON SCANNING AND FORESIGHT METHODS

Summary of Key Findings

- Horizon scanning helps in assessing whether one is adequately prepared for future changes or threats.
- If performed consistently and effectively, horizon scanning, when combined with other forecasting tools, can assist in policy making by identifying important needs or gaps.
- Horizon scanning is also an effective tool for bringing experts in different subject areas together to discuss a common issue and develop viable solutions.
- All horizon-scanning processes involve some iteration of the cyclical actions of scanning, analyzing, synthesizing, and communicating information.
- Expert input from a variety of credible sources is critical to the success of a horizon-scanning process.
- In considering a horizon-scanning process for the bioeconomy, four key questions need to be addressed:
  - Approach: Is the intent to enable scenario planning, or is it to identify specific issues that could have a policy impact?
  - Scope: Will the horizon-scanning efforts envisaged be broad (e.g., mapping issues that might affect the bioeconomy) or narrow (e.g., mapping all the issues emerging in a specific field)?

  - Process: Will the data being fed into the future-thinking process come from machine-readable sources or be based on expert opinion?
  - Timeframe: Is the intent to look at the near term, identifying issues that are emerging now, or further out, including the far horizon of 10–20 years in the future?
- Integrating horizon scanning into a broader foresight process will enable better policy making in the near term, providing for the ongoing timely identification of additional strategies that may be needed to safeguard new technologies and data, and for assessment of their implications for innovation and biosecurity.

A range of tools can be used to think about future risks and opportunities in a structured manner. As noted by Daniel Flynn from the Office of the Director of National Intelligence, these tools "are for future planning in a world where the future cannot be known."[1] Such tools are commonly used to help shape policy so that entities (such as governments or organizations) are more resilient and better placed to take effective action (IRM, 2018). As explained by the UK Cabinet Office:

> It's not about making predictions, but systematically investigating evidence about future trends. Horizon scanning helps government to analyze whether it is adequately prepared for potential opportunities and threats. This helps ensure that policies are resilient to different future environments.[2]

Horizon scanning is therefore not about predicting the future, but focused on the early detection of weak signals as indicators of potential change.

The terminology around relevant tools, techniques, and processes involved in horizon scanning has yet to be standardized, which can lead to confusion. In some cases, for example, the overall process of structured reflection on the future is referred to as "horizon scanning" (UK Government Office for Science, 2013), while in others it is termed "foresight" or "future(s) thinking" (FAO, 2013). In this report, the committee has adopted a definition similar to that used by the Organisation for Economic Co-operation and Development (OECD): horizon scanning is "a

[1]Mr. Flynn spoke during a webinar held for this study on June 11, 2019.
[2]See https://www.gov.uk/government/groups/horizon-scanning-programme-team.

technique for detecting early signs of potentially important developments through a systematic examination of potential threats and opportunities, with emphasis on new technology and its effects on the issue at hand" (OECD, n.d.a).

Horizon scanning can be integrated into a broader futures-thinking or foresight framework. This framework describes the overall broader process of assessing and understanding the policy implications of relevant developments, as well as identifying desired futures and specific policy actions that can help realize them (see Annex 6-1 for more detailed discussion of these terms). ETH Zurich developed a model foresight process as part of efforts to strengthen policy making in Switzerland (Habegger, 2009) (see Figure 6-1). This model has three phases. The first involves the identification and monitoring of relevant issues, trends, developments, and changes, accomplished using the tool of horizon scanning. The second phase is assessing and understanding the resulting policy challenges, which makes use of different tools. The third phase involves envisioning desired futures and identifying specific policy actions for realizing them, based on the development of specific scenarios.

This chapter considers horizon scanning in depth, starting with an exploration of how it is used as a policy tool. This is followed by an overview of good practices in horizon scanning. This overview considers potential sources of information, the development of criteria to parameterize the scan or to use for evaluating the outcome, and avenues for improving traditional horizon-scanning methods. Also considered are issues related to communicating the results, connecting the results to specific actions, and learning lessons from the past. To demonstrate how horizon scanning works in practice, the chapter then presents case studies of relevant scans carried out in the past, both in the United States and in other parts of the world. Several of these case studies focus specifically

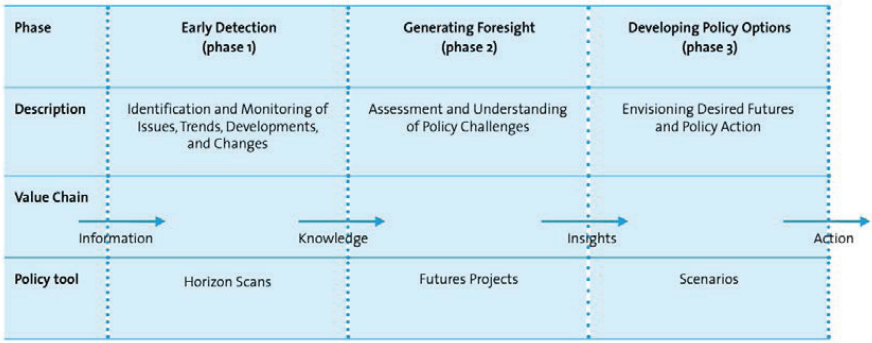


FIGURE 6-1 Three phases of a comprehensive foresight process. SOURCE: Illustration by Habegger, 2009, based on Schultz, 2006, and Horton, 1999.

on biotechnology, while others have been produced by sectors potentially relevant to this study, such as defense, health, food safety, agriculture, and environment and conservation. Next, the chapter places horizon scanning within the broader context of exploring a number of relevant toolkits, handbooks, and guidance, as well as the application of forecasting, or future thinking, by what is termed "superforecasting." The chapter ends with the committee's conclusions outlining a possible mechanism for future thinking and horizon scanning tailored to the U.S. bioeconomy, based on existing best practice and making use of current resources.

HORIZON SCANNING AS A POLICY TOOL

Horizon scanning, often as part of a foresight process, can help address a wide variety of policy-making needs (see Annex 6-1 for an overview of one such analysis). It can also generate important information (such as the identification of important trends or developments), and help gain lead time in addressing future issues or serve as an input for scenario-development processes (European Commission, 2015; OECD, n.d.a). It can help ensure that policy making incorporates "thinking outside the box" and that it is able "to manage risk by planning ahead for unlikely, but potentially high impact events" (UK Government Office for Science, 2013). More broadly, benefits accrue from bringing together experts and policy makers from different backgrounds and disciplines (Habegger, 2009). It is important to recognize, however, that horizon scanning operates beyond a firm evidence base and relies on the instincts of those involved in the exercise (UK Government Office for Science, 2017).

The process of horizon scanning can be considered to encompass two separate approaches: "Continuous scanning activities to keep the overview (often with regular newsletters), regular but discontinuous activities (e.g., every 5 years) and ad-hoc Horizon Scanning for a specific purpose, on demand or at a specific occasion" (European Commission, 2015). A number of different horizon-scanning methods have been identified. For example, the Food and Agriculture Organization of the United Nations (FAO) developed a typology that includes best–worst scanning for prioritizing trends or developments, delta scanning for capturing identified trends and developments from other horizon-scanning processes, expert consultations for tapping specialist knowledge, and manual scanning to identify signals of change to track trends and drivers. FAO also provided examples of how each of the methods is commonly used and provided indicative strengths and weaknesses for each (FAO, 2013).

Horizon scanning has been explicitly integrated into policy-making processes in some parts of the world. For example, the United Kingdom has integrated horizon scanning into its central policy making through

its Cabinet Office. The United Kingdom uses horizon scanning as part of a larger foresight process to gather information on relevant trends and developments (monitoring) and explore their possible implications. Horizon scanning is additionally used as a mechanism for engaging people in future thinking and generating an environment conducive to yielding insights into the changing policy environment. Similar efforts have been undertaken, for example, in Singapore (Chong et al., 2007), the Netherlands (European Environmental Agency, 2011), and Switzerland (Habegger, 2009). Efforts in Singapore have focused heavily on automating a horizon-scanning process.

GOOD PRACTICES IN HORIZON SCANNING

The Horizon-Scanning Process

A number of different horizon-scanning processes have been described, including by the UK Government Office for Science (2017), the European Union (EU) Directorate-General (DG) for Research and Innovation (European Commission, 2015), the Institute for Risk Management (IRM, 2018), and several academic groups (Brown et al., 2005; Habegger, 2009; Wintle et al., 2017). An example of a horizon-scanning process is provided in Figure 6-2. In general, these processes share the following features. They start by defining the scope of the scan and then identifying experts likely to have important relevant insights. For example, the IRM process emphasizes the importance of involving a diverse range of participants with open minds (IRM, 2018). Several other models stress that the process can be open-ended, involving as many people as desirable. Of course, increasing the number of people involves additional burdens in terms of tracking and compiling the results and may necessitate a dedicated project manager. Participants are then tasked with compiling a structured scan of a specific issue in a fixed timeframe. For example, the UK process suggests one scan per person per week (UK Government Office for Science, 2017). The issues to be covered can either be pre-identified or identified at the discretion of the participants, thereby drawing on their expertise and insights as to what may be relevant. Each scan describes the trend or development identified, how it relates to the policy or strategy area being explored, why the participants found it important, and what thoughts it stimulated. These descriptions can usefully contain links to original sources or additional information, but preferably are short. For example, the UK process suggests no more than one page (UK Government Office for Science, 2017).

Some processes stop at this point, and their final output is a series of collated issue scans over time, although this output is then sometimes fed

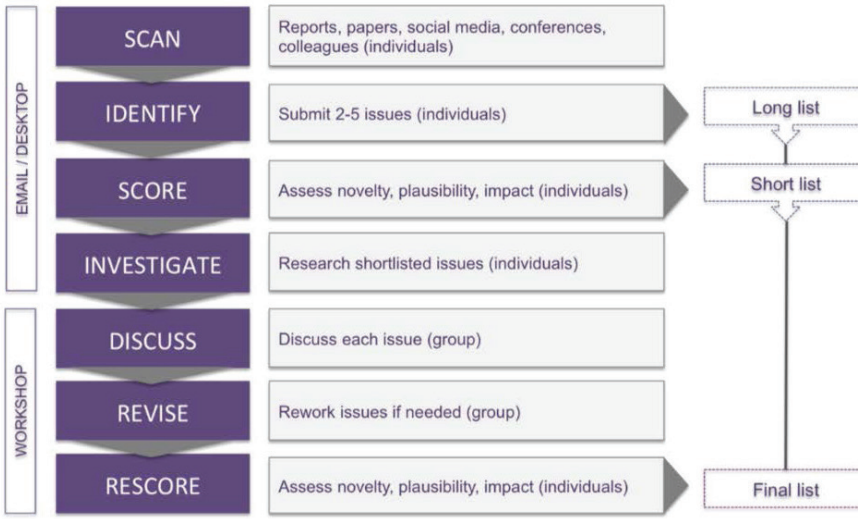


FIGURE 6-2 An example of a horizon-scanning process. SOURCE: Wintle et al., 2017.

into other activities as part of a larger process, as is the case in the United Kingdom (UK Government Office for Science, 2013). Other processes go further and provide additional steps that involve discussing, refining, rating, or otherwise reviewing the scans within the horizon-scanning process itself. For example, the process developed by the EU DG for Research and Innovation calls for expert dialogue. Some of the academic processes involve a more comprehensive semiquantitative approach, including the need for in-person interaction through a workshop (European Commission, 2015). Some processes then include additional steps to package and frame the results to facilitate their use in policy making. For example, the IRM process highlights the value of visualization (IRM, 2018).

Optimizing a Horizon-Scanning Process

Several factors, such as the sources of information, the decision criteria, methodological tools to tailor the generic process, and the policy impact need to be considered when seeking to optimize a horizon-scanning process (for more detailed discussion of each of these factors, see Annex 6-1).

Sources of information—Information for a horizon scan can come from a number of different sources. Some sources, such as publications, quantitative data, and published opinions, may be more traditional. To reach the limits of current thinking, however, less traditional sources, such as

news outlets, social media, and prepublication servers, may be needed. The process of gathering information can also be increasingly automated as the topic becomes more familiar.

Decision criteria and questions to ask—Either when developing a scan on a topic or when reviewing its potential policy impact, a range of criteria can be applied, such as credibility, novelty, likelihood, impact, relevance, time to awareness (how long before the topic or its impact is widely known), and time to prepare for the development. A number of specific questions for exploring each of these criteria have been proposed (Hines et al., 2018).

Methodological tools to tailor the generic process—A number of recent publications describe methodological tools for horizon scanning. Examples include the use of pre-developed scenarios to aid in the identification of important weak signals (Rowe et al., 2017); more structured approaches for matching specific horizon-scanning tools to the needs of policy makers, including better metrics (Amanatidou et al., 2012); the integration of more comprehensive collaborative review processes to identify appropriate responses by policy makers and practitioners (Sutherland et al., 2012); and mechanisms for assessing the value of different information sources to be used for the horizon scan (Smith et al., 2010).

Increasing the policy impact—A number of good practices for presenting and communicating the results of a horizon scan have been identified, including having a specific sponsor for horizon-scanning and futuring work; translating results in a more accessible manner; tailoring reporting to policy interests; matching timing to political timeframes; selecting experts to increase policy relevance; focusing on potential impacts of events discussed, as well as the timeframes involved; and structuring the results in a logical manner, whether by groups of issues identified or by relevant policy drivers.

Lessons Learned from Past Uses of Horizon Scanning

A number of lessons have been distilled from previous uses of horizon scanning in policy making. For example, horizon-scanning experts consulted by the committee[3] discussed (1) the use of expert opinion, (2) sources of bias and approaches to managing them, and (3) options for evaluating the effectiveness of horizon scanning.

On the use of expert opinion, the speakers observed that individuals' expertise declines dramatically outside the narrow domain of their area of technical specialization or experience, and pointed out that there is also particular value from generalist, nonexpert input. Relatedly, age, number

[3]These experts spoke at a webinar held for this study on June 11, 2019.

of publications, technical qualifications, years of experience, memberships in learned societies, and apparent impartiality do not explain an expert's ability to estimate unknown quantities or predict future events. However, a number of factors tend to lead to better judgments. An example is experts with experience in fields requiring rapid feedback, such as chess players, weather forecasters, sports players, gamblers, and intensive care physicians. People who are less self-assured and assertive and integrate information from diverse sources also make better judgments. It was noted as well that estimates of risk in many domains can be improved by weighting experts' opinions by their performance on test questions and that relevant training can improve experts' abilities to estimate probabilities of events. Lastly, group estimates consistently outperform individual estimates, and diverse groups tend to generate more accurate judgments.

On biases, the experts who spoke to the committee identified the various types of bias and suggested ways to mitigate their effects on the process and outcome of horizon scanning. *Gambler's fallacy* (the belief that past events will unduly impact future events) and the *availability heuristic* (the potential to be overly influenced by more recent memories and events) can be mitigated by identifying and unpacking assumptions inherent in the process, both in the task assigned and on the part of those involved. *Confirmation bias* (the likelihood of searching for, interpreting, focusing on, and remembering information that confirms preconceptions) can be mitigated by involving participants from a wide range of backgrounds and expertise, drawn from different communities and locations. *Projection bias* (the belief that preferences will remain the same over time) can lead to focusing on only a subset of issues or options. It can be mitigated by unpacking assumptions and questioning them, as well as by expanding the range of expertise involved in the process. The *bandwagon effect*, or "groupthink," increases the likelihood of failing to explore the full range of options or issues, and can be countered by deliberately involving experts from diverse backgrounds and communities. *Anchoring bias* (the tendency to rely too heavily on a single piece of information, which is often the first obtained) can be mitigated through the use of advocates both for and against a specific issue, as well as multiple rounds of scoring in different orders. Finally, s*alience bias* (the likelihood of focusing on something more prominent or emotionally impactful, especially when particularly vocal or skilled raconteurs are advocating for specific issues) can be managed through rules on advocating positions that are consistently and rigorously enforced, as well as the use of voting and anonymous feedback.

On evaluating the effectiveness of horizon scanning, the experts commented that attempts have been made to review the impact of past horizon scans. As might be expected, these efforts have demonstrated that some

issues were identified in a timely manner and deemed impactful, while others that were identified ultimately had a minimal impact (Sutherland et al., 2012). However, given that horizon scanning is not about predicting the future, assessing the "hit rate" of predictions is an inappropriate metric. The absence of an event is not necessarily the absence of impact. Identifying an early signal and taking effective policy action may result in an apparent null outcome. Metrics for a horizon-scanning or futuring effort might therefore be focused more usefully on exploring whether the effort led policy makers to consider more issues or explore more options. Alternatively, useful insights might be gained by comparing the assessments resulting from a horizon scan against those resulting from other tools with respect to facilitating better policy making.

Publications from other entities, such as the National Intelligence Council (NIC, 2017), the U.S. Forest Service (Hines et al., 2018), the UK government (UK Government Office for Science, 2017), and the EU (European Commission, 2015), have documented reflections, key considerations, rules for implementation, and improvements made through iterative use of horizon scanning (see Annex 6-1 for a detailed discussion of lessons learned).

CASE STUDIES OF HORIZON SCANNING

A number of horizon scans relevant to this study have already been carried out. Both the content of these scans and the communities that produced them could serve as important resources moving forward. The committee noted a paucity of documented horizon-scanning activities performed by U.S. federal agencies. Should relevant federal agencies be carrying out these activities, there is considerable room to enhance transparent reporting of and sharing of experiences from those efforts.

This section provides examples of past scans and the actors undertaking them. The scans reviewed include those directly connected to the bioeconomy, those conducted within the U.S. Intelligence Community, those carried out by agencies with a direct role to play in safeguarding the bioeconomy, and those conducted within a U.S. federal agency. Examples of additional horizon scans are described in Annex 6-1, including efforts that have brought together separate horizon scans from different agencies and subject-specific scans in areas related to the bioeconomy, such as health, food safety, and the environment and conservation.

Example of a Horizon Scan Connected to the Bioeconomy

In 2017, a transatlantic horizon scan was published describing developments in biological engineering likely to have substantial impacts on global society. The process brought together experts in horizon scanning,

biosecurity, plant biotechnology, bioinformatics, synthetic biology, the bioeconomy, biodefense, science policy, nanotechnology, conservation and environmental sciences, industrial biotechnology, and the social sciences. These experts used the process described in the section above on the horizon-scanning process to identify 70 potential issues and then prioritized 20 of these issues, covering such sectors as health, energy, agriculture, and the environment (Wintle et al., 2017) (see Table 6-1).

The 20 prioritized issues were categorized according to their likely timeline for impact. Highlighted as likely to have an impact within 5 years were five issues, including novel approaches to gene drives (which subsequently received notable backing for development from major science

TABLE 6-1 Issues in Biological Engineering Likely to Have Substantial Impacts on Global Society in the Short, Medium, and Long Terms

Issues Likely to Impact Within 5 Years	Issues Likely to Impact in 5–10 Years	Issues Likely to Impact in More Than 10 Years
• Artificial photosynthesis and carbon capture for producing biofuels • Enhanced photosynthesis for agricultural productivity • New approaches to synthetic gene drives • Human genome editing • Accelerating defense agency research in biological engineering	• Regenerative medicine: 3D printing of body parts and tissue engineering • Microbiome-based therapies • Producing vaccines and human therapies in plants • Manufacturing illegal drugs using engineered organisms • Reassigning codons as genetic firewalls • Rise of automated tools for biological design, test, and optimization • Biology as an information science: impacts on global governance • Intersection of information security and bioautomation • Effects of the Nagoya protocol on biological engineering • Corporate espionage and biocrime	• New makers disrupt pharmaceutical markets • Platform technologies to address emerging disease pandemics • Challenges to taxonomy-based descriptions and management of biological risk • Shifting ownership models in biotechnology • Securing the critical infrastructure needed to drive the bioeconomy

SOURCE: Adapted from Wintle et al., 2017.

funders) (Wellcome Trust, 2017), human genome editing (2018 saw the birth of the first genome-edited babies) (Cyranoski and Ledford, 2018), and accelerated defense agency research (with novel research programs causing debate within the biosecurity community on the desirability of such research) (Lentzos and Littlewood, 2018). Ten issues were deemed likely to have an impact in 5–10 years, including cyberbiosecurity and corporate espionage and biocrimes (which are directly connected to the aims of this study). Finally, five issues were identified as likely to have an impact in more than 10 years, including securing critical infrastructure needed to deliver the bioeconomy.

Example of Horizon Scanning Within the U.S. Intelligence Community

Shortly after the start of each presidential term, NIC publishes "an unclassified strategic assessment of how key trends and uncertainties might shape the world over the next 20 years to help senior U.S. leaders think and plan for the longer term" (NIC, 2017). Comparatively few details are publicly available about the precise methodology used by NIC, but according to the NIC (2017) report, it involved desk research as well as consultations with experts from inside the U.S. government and from around the world. This enabled the identification of, and subsequent reflection on, key assumptions and trends. Assessment of implications was first carried out at the regional level before being aggregated to identify global trends. The results were structured over different timeframes, ranging from the near term (5 years) to the long term (20 years). Analytic simulations were used to explore future scenarios, in particular how uncertainties and trends might combine to alter outcomes.

The scale and breadth of the consultations reported were also noteworthy:

> Ultimately, our two-year exploration of the key trends and uncertainties took us to more than 35 countries and meetings with more than 2,500 individuals—helping us understand the trends and uncertainties as they are lived today and the likely choices elites and non-elites will make in the face of such conditions in the future. Visits with senior officials and strategists worldwide informed our understanding of the evolving strategic intent and national interests of major powers. We met and corresponded with hundreds of natural and social scientists, thought leaders, religious figures, business and industry representatives, diplomats, development experts, and women, youth, and civil society organizations around the world. We supplemented this research by soliciting feedback on our preliminary analysis through social media, at events like the South by Southwest Interactive Festival, and through traditional workshops and individual reviews of drafts. (NIC, 2017)

These expert interviews and the feedback received were then integrated into a scenario-based, policy-oriented foresight approach. The scenario work and backcasting efforts were used to identify choices and policy decisions that could help realize desirable futures and avoid the undesirable (NIC, 2017). Specific tools used in the preparation of the NIC report that might be important for forecasting work relevant to this study include net assessment and analytic simulations. Net assessment is

> a systematic method of analysis that fulfils the need for an indirect decision support system and provides a major input to the strategic planning/management system in the Department of Defense. Through an established process of appraising two or more competitors as objectively as humanly possible, an analyst is guided to examine factors normally overlooked. Asymmetries that exist among competitors and the ability of a competitor to achieve its objectives in various conflicts are examples of some of these factors. (Konecny, 1988)

Net assessment "uses data that are widely available and creates strategic insights that lead to decisive advantage. It offers paths through the increasingly dangerous landscape of national security." It often makes use of a specific set of tools. "Scenarios, war games, trend analysis, and considered judgment are the methods most widely used in net assessment studies and analyses" (Bracken, 2006).

Analytic simulations, including historical wargaming and analytic path games, have proven useful in military planning for future conflicts. They have allowed commanders to plan for the unknown by both better understanding adversaries and preparing possible responses in advance of events.[4]

Example of Horizon-Scanning Tools Being Developed by an Agency Connected to Safeguarding the Bioeconomy

In 2015, the Office of Technical Intelligence in the U.S. Department of Defense published an assessment of data analytics–enabled technology watch and horizon scanning (TW/HS) for the identification, characterization, and forecasting of known and unknown science, technology, and applications (Office of Technical Intelligence, 2015). According to the assessment report, "data-enabled TW/HS has the potential to improve upon or augment current approaches by expanding the aperture of analyses and decreasing the influence of bias, while at the same time building

[4]This observation was made by a participant in the committee's webinar on June 11, 2019.

institutional capacity." The report includes a structured framework for integrating new technologies (such as data analytic tools) into existing workflows. This framework reflects components of the generic horizon-scanning process described earlier, including the following (all descriptions are from Office of Technical Intelligence [2015]):

Characterizing decisions (see the above discussion of criteria and questions to ask)—Those undertaking the scan need an understanding of the decision itself; the timeline governing their work; and, most important, the evaluation criteria. This understanding "informs the scope, scale and context of the supporting analysis, which enables analysts to provide targeted, actionable inputs into the decision process in time for the information to be actionable."

Selecting data (see the above discussion of sources of information)—This process "requires careful balancing of relevance and breadth. It is critical to identify sources that are likely to provide signals relevant to the evaluation criteria and to maximize the signal to noise ratio."

Selecting metrics (see the above discussion of methodological tools and lessons learned from past uses of horizon scanning)—"Evaluation criteria are often complex human ideas which cannot be precisely calculated from data. For example, analytics cannot directly assess the maturity of a technology, but they could analyze the amount of activity which references the technology, growth rates of activity, or identify whether sources discuss prototyping or advanced testing to inform a technology readiness level estimation."

Conducting analysis (see the above discussion of decision criteria and questions to ask)—"To enable more effective application of metrics, it is often valuable to develop a taxonomy of the field under consideration. Taxonomies allow for the identification of areas at the same level of abstraction."

Developing decision support products (see the above discussion of increasing policy impact)—"Analysts must integrate the disparate portions of their findings into a cohesive whole in order to make their efforts useful to decision makers… [this] requires understanding what is useful to the decision maker, such as whether the individual metrics or a composite score would be most useful and how to communicate the findings so that they are both clear and most likely to be used effectively."

Leveraging knowledge management (see the above discussions)—"In order to move from a successful TW/HS *project* to a TW/HS *program*, it is important to ensure that products can be kept up to date with manageable amounts of effort and to track the accuracy of analysis."

Example of a Horizon Scan in a U.S. Federal Agency

In 2018, the U.S. Forest Service's Strategic Foresight Group and the University of Houston's Foresight Program published a summary of their efforts "to develop an ongoing horizon scanning system as an input to developing environmental foresight: insight into future environmental challenges and opportunities, and the ability to apply that insight to prepare for a sustainable future" (Hines et al., 2018). The process adopted was similar to that described earlier. It included an initial framing phase in which the domain of interest was mapped (including the identification of key activities, stakeholders, and drivers of change), geographic and timeframe boundaries were set, relevant stakeholders and participants were identified, and guiding questions were developed. The scan itself used a four-step process:

- Find: identify where and how to look for scanning hits.
- Analyze: use cross-level analysis and cross-layered analysis.
- Frame: develop a framework for organizing insights.
- Apply: use the results in work processes.

The criteria used in the scan to determine the relevance of an issue were those described earlier in the discussion of criteria and questions to ask. The authors identify a number of specific lessons learned from attempting to develop a horizon-scanning process within a U.S. federal agency. The study also includes a discussion of future plans for improving the communication of results, integrating the results into the host organization, and linking the results to effective action, as well as making the process self-sustaining.

Examples of Environment- and Conservation-Related Horizon Scans

One example of an international horizon-scanning effort related to the environment and conservation is a 2016 international study by academic authors from 11 countries that focused on issues likely to impact pollinators and pollination positively or negatively in the future and that succeeded in identifying six high-priority issues and nine secondary issues (Brown et al., 2016). A second example is a 2018 international study by academic authors from six countries that identified "15 emerging priority topics that may have major positive or negative effects on the future conservation of global biodiversity, but currently have low awareness within the conservation community" (Sutherland et al., 2019). The latter

is the tenth annual review conducted by this group, and its methodology was employed in the scan of biological engineering described previously.

ADDITIONAL TOOLS FOR FUTURE THINKING

In practice, horizon scanning is rarely used in isolation, but is often combined with a range of other tools and techniques. Sometimes, these tools and technique are combined into a stand-alone exercise (such as the integration of Delphi, a consultation process to gather input from a wide variety of experts and sometimes prioritize the results, and other expert review processes discussed in Annex 6-1). Alternatively, horizon scanning can be embedded in a more comprehensive foresight process that feeds the results of the scan into processes for assessing and understanding the consequent policy challenges, connecting them to possible future scenarios, and identifying specific policy actions designed to steer toward desirable outcomes. See Annex 6-1 for further detail on the additional tools discussed here.

Forecasting Tools

Several studies have catalogued a comprehensive range of forecasting tools. For example, the *Handbook of Technology Foresight*, published in 2008, explores in depth 19 qualitative tools, 8 quantitative tools, and 9 semi-quantitative tools (Popper, 2008) (see Table 6-2). FAO outlined a similar list of tools in 2014, providing a description of each tool, examples of its common use, and its particular strengths and weaknesses (FAO, 2013). And OECD has highlighted four tools as being particularly important: the scenario method, the Delphi method, horizon scanning, and a trends impact analysis (OECD, n.d.a). Many of these tools have been combined into frameworks for forecasting. Box 6-1 describes an example developed by the UK Government Office for Science.

Superforecasting

In 2010, the Intelligence Advanced Research Projects Agency (IARPA) initiated a competition to explore how crowdsourcing can improve forecasting.[5] Various tools and approaches for making accurate predictions were tested over 4 years of tournaments. IARPA identified a number of

[5]See IARPA's Aggregative Contingent Estimation at https://www.iarpa.gov/index.php/research-programs/ace/baa.

TABLE 6-2 Foresight Tools Identified by Academic Studies and Intergovernmental Organizations

Qualitative Foresight Tools	Quantitative Foresight Tools	Semiquantitative Foresight Tools
Backcasting[a,b]	Agent-based modeling[a,b]	Cross-impact/structural analysis[a,b]
Brainstorming[a,b]	Benchmarking[a]	
Citizens panels[a,b]	Indicators[a]	Delphi method[a,b,c]
Conferences/workshops[a,b]	Bibliometrics[a]	Key/critical technologies[a,b]
Essays/scenario writing[a]	Patent analysis (e.g., technology forecasting)[a,b]	Multicriteria analysis[a,b]
Expert panels[a,b]	Time-series analysis (e.g., trends)[a,b,c]	Polling/voting[a]
Genius forecasting[a]		Quantitative scenarios/ cross-impact systems and matrices[a,b]
Literature review[a]		
Morphological analysis[a,b]		
Relevance trees/logic charts[a,b]	Econometrics[a]	Roadmapping[a,b]
Role play/acting[a]	Simulation models[a]	Stakeholder analysis[a]
Horizon scanning[a,b,c]	System dynamics[b]	Mixing econometrics, simulation models, and qualitative methods[a]
Scenario workshops[a,b,c]		
Science fictioning[a]		
Simulation gaming [a,b]		
Surveys[a]		
SWOT (strengths, weaknesses, opportunities, and threats) analysis[a,b]		
Weak signals/wildcards[a]		
Assumption-based planning[b]		

[a]Identified in the *Handbook of Technology Foresight* (Popper, 2008).
[b]Identified by the UN Food and Agriculture Organization (FAO, 2013).
[c]Identified by the OECD (OECD, n.d.a).
SOURCES: Compiled from FAO, 2013; OECD, n.d.a; and Popper, 2008.

promising tools, but also concluded that (1) some individuals were notably better at making predictions than others, and (2) it is possible to learn how to be better at making predictions. These two conclusions formed the basis of what was to become known as superforecasting. A superforecasting program brings together those with a proven track record in making predictions in a system designed to enhance their abilities and in making use of tools to help interpret the results. Since the conclusion of this program, a successful team of established superforecasters has created the Good Judgment project, which offers superforecasting capabilities and training for commercial entities and public processes.[6]

[6]See https://goodjudgment.com.

BOX 6-1
The UK Government Office for Science's Futures Toolkit

In 2017, the UK Government Office for Science published a Futures Toolkit to help standardize future thinking across the UK government (UK Government Office for Science, 2017; see Annex 6-1 for additional detail). A set of tools in the kit is structured around four tools commonly used for foresight. One of those tools is closely aligned with the use envisaged in this study—to gather intelligence about the future. In addition to horizon scanning, the toolkit identifies seven questions ("an interview technique for gathering insights of a range of stakeholders"), issue papers, and Delphi processes as being useful (UK Government Office for Science, 2017). Additional tools are then used depending on the intended output of the futures process. Two of the model pathways included in the toolkit accord with the charge to this committee (Box 1-1 in Chapter 1): identifying futures research and evidence priorities, and identifying and prioritizing future opportunities and threats for action. The additional tools used for these pathways include driver mapping, roadmapping, and SWOT (strengths, weaknesses, opportunities, and threats) analysis.

Roadmapping

Roadmapping "shows how a range of inputs—research, trends, policy interventions, for example—will combine over time to shape future development of the policy or strategy area of interest" (UK Government Office for Science, 2017). A wide range of countries and regions have developed roadmaps for their bioeconomy.[7]

In 2019, the Engineering Biology Research Consortium published "Engineering Biology: A Research Roadmap for the Next-Generation Bioeconomy." This roadmap was "intended to provide researchers and other stakeholders (including government funders) with a compelling set of technical challenges and opportunities in the near and long term." It covers four technical themes and explores five application sectors (see Box 6-2).

CONCLUSIONS

During the committee's webinar on horizon-scanning methodologies, experts highlighted four key questions to consider when developing a horizon-scanning process.

[7]See, for example, https://gbs2018.com/resources/other-resources.

BOX 6-2
Technical Themes and Application Sectors Addressed in the Engineering Biology Research Roadmap

Technical Themes

- Engineering DNA
- Biomolecular engineering
- Host engineering
- Data science

Application Sectors

- Industrial biotechnology
- Health and medicine
- Food and agriculture
- Environmental biotechnology
- Energy

SOURCE: Compiled from EBRC, 2019.

- ***Approach:*** *Does the activity need to enable scenario planning, identify specific issues that could have a policy impact, or both?*
- ***Scope:*** *Will the horizon-scanning efforts envisaged be broad (e.g., mapping issues that might affect the bioeconomy) or narrow (e.g., mapping all the issues emerging in a specific field)?* A broad scope will require interacting with a wide variety of experts, while a narrow scope can more readily be attempted using published resources and desk research.
- ***Process:*** *Will the data being fed into the future-thinking process come from machine-readable sources or be based on expert opinion?*
- ***Timeframe:*** *Is the intent to look at the near term, identifying issues that are emerging now, or further out, including the far horizon of 10–20 years in the future?*

Following discussion of the above questions, the committee concluded that best practices for horizon scanning include the considerations laid out below.

Conclusion 6-1: ***Approach:*** **Policy making for the bioeconomy will be facilitated by both scenario planning and the identification of issues that could have a policy impact. Therefore, future horizon scanning will need to use at least two different approaches.**

Ongoing horizon scanning might be integrated into the work of different agencies with specific fields of expertise, using the good practices discussed in this chapter. Encouraging such agencies to share their experiences with each other would help to build relevant capacity as quickly as possible. In some cases, horizon scanning for important policy issues may already be under way. Different issues identified in these field-specific scans could then be fed into a centralized meta-review. This approach would make use of good practice in horizon scanning (as described in this chapter) to compare different issues using a common set of criteria and scoring systems and multiple rounds of voting. These ongoing activities could form the basis of a regular report, similar to NIC's Global Trends report.

Conclusion 6-2: ***Scope:*** **In general, the bioeconomy is broad and cuts across different technical fields, agencies' work, and communities. The U.S. bioeconomy is currently insufficiently characterized to consider a comprehensive mapping exercise. Broad horizon-scanning efforts might help further map the bioeconomy. In the meantime, it is possible that narrowly focused horizon-scanning activities could help answer specific policy questions.**

One-off horizon scans could be used to answer specific questions or drill down into specific issue areas. Such a process might follow an approach similar to that of the example horizon scan presented earlier in Figure 6-2. It would include modified use of the Delphi method to highlight issues considered most likely to have a policy impact, or highly novel issues that are likely to be omitted from policy-making processes. One issue that could greatly benefit from both one-off horizon scans and continued assessment is the creation and maintenance of bioeconomy-specific satellite accounts (see Chapter 3 for further detail). This combined approach is particularly suitable for the creation of satellite accounts as it serves a policy need, and the bioeconomy is continually changing.

Conclusion 6-3: ***Process:*** **Given the need to better understand the bioeconomy and factors that may affect it, future-thinking processes are likely to be human-driven in the near term, but there will be opportunities to automate part of the process as improved data sources and metrics become available.**

While these horizon-scanning processes are likely to be expert-driven, tools for automated data gathering are advancing and could be integrated into the methodology used for a horizon scan as appropriate. It will be important to involve the widest possible range and diversity of expertise.

The meta-review process, resources permitting, might resemble the scope, scale, and nature of NIC's Global Trends report, aiming to directly engage thought leaders from different communities around the world.

Criteria to be applied in assessing potential issues to be fed into horizon scans include *credibility* (e.g., Is the source reputable? Is it confirmed elsewhere?); *novelty* (Is the issue new, or has it already been widely reported?); *likelihood* (What are the chances the issue will actually occur?); *impact* (Will the issue change the future, and if so, how big will that change be?); *relevance* (How relevant is the issue to the bioeconomy, and is that relevance direct or indirect?); *time to awareness* (How long is it likely to be before the issue is widely known, and could this change [or be changed]?); and *time to prepare* (When is the issue likely to have an impact, what could affect its impact, and when would that intervention need to take place?).

Conclusion 6-4: *Timeframe:* Given the framing of horizon scanning as a tool for identifying weak signals as early as possible, a notable focus will need to be placed on the longer term. By integrating horizon scanning into a broader foresight process, it will be possible to identify policy options in the near term that could help realize desirable future scenarios and avoid the undesirable. The intent would not be to use the longer-term timeframe of horizon scanning as an excuse to avoid efforts to strengthen policy making in the interim, including the recommendations included in this report.

The above conclusions represent the committee's view of elements for a future-thinking and horizon-scanning mechanism for the bioeconomy. A structured foresight process making use of horizon scanning would help support policy making around the future of the bioeconomy. Chapter 8 considers the establishment of a government-wide mechanism to monitor and oversee the U.S. bioeconomy. Future thinking and horizon scanning should be a tool at this network's disposal.

Conclusion 6-5: To be effective, a structured foresight process making use of horizon scanning would need a champion with the resources to sustain such an activity, influence to feed the results into appropriate policy-making processes, and leadership buy-in to ensure that neither the process nor its results would be sidelined.

Foresight processes build on horizon scanning intended to identify issues that could have a policy impact, feeding into assessment and scenario-based processes for exploring policy options. How horizon scanning is integrated into broader foresight activities will depend on the ultimate purpose at hand. The committee's Statement of Task on horizon

scanning includes both (1) identifying gaps in terms of new technologies, markets, and data sources that could provide insights into the bioeconomy; and (2) identifying and helping to prioritize opportunities and threats with respect to safeguarding the bioeconomy. A structured, flexible, and adaptive foresight process is key to identifying additional strategies that might be needed to safeguard these new technologies and data and assess their implications for innovation and biosecurity. A model for such a foresight process that embraces both tasks can be found in two of the pathways included in the UK Government Office for Science's Futures Toolkit (see Box 6-1): identifying future research and evidence priorities and identifying and prioritizing future opportunities and threats for action. These pathways could usefully be adapted to take advantage of existing foresight resources and approaches and other tools in use within the U.S. government.

Conclusion 6-6: Foresight processes can be used to identify gaps in new technologies, markets, and data sources in addition to identifying and helping to prioritize opportunities and threats for safeguarding the bioeconomy.

The aim of this process, which would need to be integrated into the specific questions asked of participants, would include identifying "known unknowns" and previously "unknown unknowns." It would be used to begin to formulate hypotheses about the future of the bioeconomy and to shape future research agendas. It would use desk research, interviews, and workshops to produce an evolving roadmap showing how the issues identified could impact the bioeconomy over time. Such a process would need to involve both subject-matter experts and policy makers responsible for relevant areas (see Annex 6-1 for more detail on exactly what such a process might entail).

Horizon-scanning activities would be fed into driver mapping, which could be used to categorize, but not prioritize, drivers. The results of this activity would then be subjected to SWOT (strengths, weaknesses, opportunities, and threats) analysis. That analysis might usefully identify whether the threat or opportunity will impact the bioeconomy in the short, medium, or long term; the potential outcome or implications for the bioeconomy; whether there are control measures that could be implemented; what actions could be taken directly or indirectly to mitigate threats or seize opportunities; and with whom it will be necessary to work to deliver that action. Likely timeframes and impacts also might usefully be addressed using superforecasters. Possible actions, partners, and control measures might be explored using net assessment and analytic pathway games.

Annex 6-1
Defining Horizon Scanning

In this report, the committee uses the terms "horizon scanning" and "future thinking"/"foresight" as developed by the Organisation for Economic Co-operation and Development (OECD):

- Horizon scanning is "a technique for detecting early signs of potentially important developments through a systematic examination of potential threats and opportunities, with emphasis on new technology and its effects on the issue at hand" (OECD, n.d.a).
- Futures thinking is "a method for informed reflection on the major changes that will occur in the next 10, 20 or more years in all areas of social life … [and] uses a multidisciplinary approach to pierce the veil of received opinion and identify the dynamics that are creating the future. While the future cannot be reliably predicted, one can foresee a range of possible futures and ask which are the most desirable for particular groups and societies. A variety of methods—qualitative, quantitative, normative, and exploratory—help illuminate the possibilities, outline policy choices, and assess the alternatives" (OECD, n.d.b).

Use of these definitions is consistent with their use in other settings. The Food and Agriculture Organization of the United Nations (FAO), for example, notes that horizon scanning "generally refers to methodological approaches that scan or review various data sources, while Foresight generally refers to the wider group of more participatory methods" (FAO, 2013).

There have been numerous other attempts to define horizon scanning (European Commission, 2015; IRM, 2018; OECD, n.d.a; UK Government Cabinet Office, 2013). Common components of these definitions include that the tool

- makes use of a standardized, systematic methodology, including a specific set of criteria in the searching or filtering processes to ensure that the results are relevant to the scan's stated aim (FAO, 2013; OECD, n.d.a; UK Government Cabinet Office, 2013; UK Government Office for Science, 2013);

- focuses on emerging trends rather than specific events or discoveries—such as the trend toward more efficient genome engineering compared with the specific discovery of clustered regularly interspaced short palindromic repeats (CRISPR) as a means of achieving that trend—especially trends that challenge existing assumptions (OECD, n.d.a; UK Government Cabinet Office, 2013);
- utilizes specified data repositories or other sources of information (OECD, n.d.a; UK Government Cabinet Office, 2013);
- attempts to differentiate among types of signals, whether they be constants, changes and constant changes, or weak (or early) signals, as well as trends and wild cards (OECD, n.d.a; UK Government Cabinet Office, 2013);
- looks further ahead than the standard electoral cycle, often into the medium or longer term (UK Government Cabinet Office, 2013; UK Government Office for Science, 2013); and
- results in conclusions that can be tied to specific actions or otherwise be fed directly into policy-making processes (FAO, 2013; OECD, n.d.a; UK Government Cabinet Office, 2013; UK Government Office for Science, 2013).

HORIZON SCANNING AS A POLICY TOOL

According to the Institute for Risk Management, horizon scanning is used as a tool

- "To deepen the understanding of the driving forces affecting future development of a policy or strategy area;
- To identify gaps in understanding and bring into focus new areas of research required to understand driving forces better;
- To build consensus amongst a range of stakeholders about the issues and how to tackle them;
- To identify and make explicit some of the difficult policy choices and trade-offs that may need to be made in the future;
- To create a new strategy that is resilient because it is adaptable to changing external conditions; and
- To mobilize stakeholders to action" (IRM, 2018).

The European Union (EU) Directorate-General (DG) for Research and Innovation has outlined a series of considerations for developing a horizon-scanning process (European Commission, 2015):

- purpose—from providing independent advice as an input to a policy process through legitimizing existing policy decisions;
- scope—from providing an overview of an uncharacterized field through exploring a predefined field;
- degree of automation—from an automated process through an expert-driven exercise;
- duration—from an on-demand activity through an ongoing process; and
- integration—from being a stand-alone activity through being part of a broader policy-making process.

The EU DG notes that determining the needs of a specific horizon-scanning process for each of these considerations will likely have implications for how focused the results will be. The specific needs of each category will also determine the time and resources required (European Commission, 2015).

The United Kingdom provides an example of horizon scanning in policy making, having integrated horizon scanning into its central policy making through its Cabinet Office. The UK process considers three policy horizons (see Figure Annex 6-1). Horizon 1 relates to impacts that will be felt today and tomorrow, where "trends and events stand out against the background and their impacts are clearly signaled to policy makers." These trends and events can be addressed by actions currently being taken. Horizon 2 comprises trends whose impact will be seen in the short to medium term and can be fed into strategic thinking. Horizon 3 encompasses those trends that will grow in importance in the longer term, for which some planning may be needed. The UK process frames horizon scanning as a tool that "looks towards the long term (Horizon 2 to 3) but is not focused exclusively on it; many H3 developments are the long-term outcome of a range of factors, some of which are in play already" (UK Government Office for Science, 2017).

GOOD PRACTICE IN HORIZON SCANNING

Factors to be considered when developing a horizon-scanning process include sources of information, criteria and questions used to explore them, and policy impact.

Sources of Information

Information for a horizon scan can come from a wide variety of sources, and needs to be tailored to the area of interest of the individual process. Information sources can be traditional, such as publications,

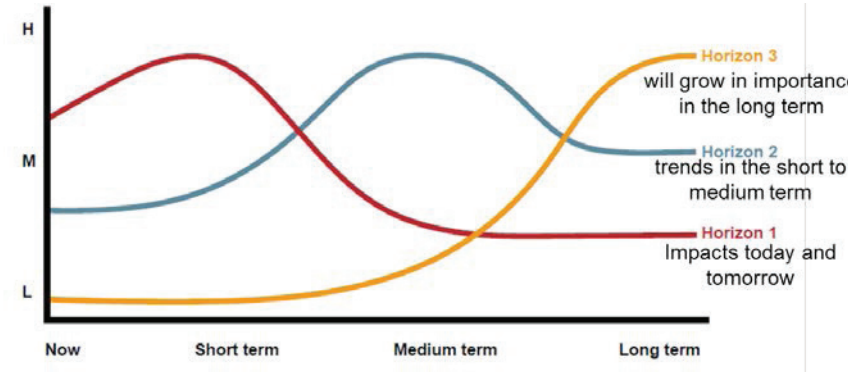


FIGURE ANNEX 6-1 The United Kingdom's three-horizons model for future thinking representing short-, medium-, and long-term timescales of outlook. SOURCE: UK Government Office for Science, 2017.

quantitative and qualitative data, and published expert opinions, but it is equally important to consider unique sources that fall on "the margins of current thinking," ensuring a holistic perspective (Habegger, 2009). As a result, sources can also be less traditional, such as news outlets, social media, and prepublication servers. In addition, the process may need to take into account insights into lifestyles, people's sociological expectations, or other indicators of potential impact. It will often benefit from including insights from key stakeholders, such as those provided by professional bodies, industry leaders, customers, or those working in the field in question. It is also possible to apply semiquantitative approaches to rating the utility of different sources (Smith et al., 2010).

Efforts are under way to move from manual compilation of information using experts to more automated models. For example, Singapore established the Risk Assessment and Horizon Scanning Experimentation Center to develop better tools for data analytics, modeling, and perspective sharing (Chong et al., 2007). Efforts have been made as well to adapt advances in agent-based modeling in order to automate some of the analysis of the output from horizon scans (Frank, 2016).

Criteria and Questions Used to Explore Them

When a scan of a short timescale on a specific topic is being prepared, it is important for it to describe the trend or development identified,

explain how it relates to the policy or strategy area being explored, and detail why the trend or development is believed to be important and what thoughts it stimulated. The process can include links back to supporting materials and additional information.

To ensure comparability, some processes suggest that those participating in a horizon scan attempt to frame the issues at a similar level of granularity. For example, very specific developments might have a profound impact in one area but be much less likely to have an impact at the level of a policy development. On the other hand, overgeneralization may offer policy relevance but lack specific ties to trends or developments specific enough to be targeted by policy actions (Wintle et al., 2017). Either when developing a scan on a topic or when reviewing its potential policy impact, a number of specific criteria have been suggested, and specific questions have been proposed for exploring each criterion (see Table Annex 6-1) (Hines et al., 2018).

There are also more quantitative approaches for comparing criteria. For example, an analytic hierarchy process can be used to weight the criteria applied in a horizon-scanning exercise (Mehand et al., 2018; WHO, 2017).

Policy Impact

During the committee's webinar on horizon scanning, speakers indicated the importance of having a specific sponsor for horizon-scanning and futuring work. A sponsor would need to have the resources to sustain relevant work, the ability to feed the results into relevant policy-making processes, and a high-level interest in the work to ensure that neither the process nor the conclusions of the horizon scan would readily be sidelined. Speakers also discussed the importance of carefully considering how the output from foresight processes might best be used to inform decisions, i.e., how the future can be used to inform today's decisions. That process would likely involve creating a narrative for the future, including through different storytelling approaches. It is also useful to use backcasting (starting with a desirable future and working backwards to highlight decisions and actions that connect it to the present).[8]

The EU has stressed the importance of people in translating the results of a horizon scan into action. It suggests that while parts of the process might be automated, expert involvement is likely to result in more policy-relevant output. It also stresses the importance of understanding who might take action as a result of the scan, what their drivers and priorities

[8]Webinar 3, 2019, at http://nas-sites.org/dels/studies/bioeconomy/webinars.

TABLE ANNEX 6-1 Criteria and Questions to Be Considered When Conducting a Horizon Scan

Criterion	Questions
Credibility	Is the source reputable?
	Are there confirmations elsewhere?
Novelty	Is the hit new?
	Or has it been widely reported?
	Is it new to the client/audience?
Likelihood	What are the chances that the hit will occur, and that it will amount to something?
Impact	Will it change the future?
	If it does change the future, how big a change will that be?
Relevance	How important is that change to the client or the domain?
	Is the relevance direct or indirect?
Time to awareness	How long before this information is widely known?
	When will it appear in a mainstream newspaper or magazine?
	Are there resources to influence the potential outcome suggested by the hit?
Time to prepare	How long before this hit begins to change the future?
	Is it too late to do anything about it?
	Is it so far off that action now would be premature?

SOURCE: Adapted from Hines et al., 2018.

are, and a clear plan to engage them (or ensure their buy-in from the start) (European Commission, 2015).

The Institute for Risk Management recommends developing a framework for categorizing separate scans to facilitate comparing and reviewing them. It also stresses the importance of highlighting the potential impact of the events and trends identified, in particular describing potential risks and time to impact, which should help an end user better understand the need to take action and how fast it is necessary to act (IRM, 2018).

In its Futures Toolkit, the United Kingdom further elaborates on the importance of a framework for categorizing scans. It proposes two possible approaches: either structuring them according to different change

drivers, such as political, economic, societal, technological, legislative, or environmental factors; or preferably grouping them by themes that emerge from the scans themselves. The toolkit highlights two different formats for presenting the results of a scan: a longer narrative summary providing an overview, broad implications, and specific policy implications; and a shorter structured summary providing a few simple details of impacts, issues, and implications (UK Government Office for Science, 2017).

CASE STUDIES OF HORIZON SCANNING

Examples of Health-Related Horizon Scans

There have been numerous efforts to use horizon scans to identify and prioritize emerging technology in the health sector. Some examples are published snapshots of a single horizon scan, while others are ongoing monitoring processes, and a few track trends in the use of these tools. Examples include the following:

- A joint project of the governments of Australia and New Zealand assessed the potential impact of emerging technologies on public health systems (HealthPACT, 2011).
- A review focused on how horizon scanning has been used to help determine the suitability for public subsidy of new and emerging medical technologies in the Australian private health care sector (O'Malley and Jordan, 2009).
- The Canadian Agency for Drugs and Technologies in Health conducts a horizon-scanning process to identify and monitor new and emerging health technologies that are likely to have a significant impact on the delivery of health care (CADTH, 2015).
- A 2012 review focused on different horizon-scanning approaches used in the United Kingdom's health system (Miles and Saritas, 2012).
- A 2016 review of the use of forecasting tools identified emerging medical health technologies. The study identified 15 relevant efforts and noted that almost all relied on expert opinion, and only 2 used more complex processes, such as scenario development (Doos et al., 2016).
- A 1999 review examined how horizon scanning can help the United Kingdom's National Health Service identify and evaluate new technologies and select the most important ones for further support (Stevens et al., 1999).

- A 2003 joint Danish and UK effort was undertaken to analyze how the Internet is used by horizon-scanning systems to systematically identify new health technologies (Douw et al., 2003).

Examples of Food Safety–Related Horizon Scans

FAO identified several organizations that have conducted or continue to regularly conduct horizon scans for food safety (FAO, 2013):

- **Canadian Food Inspection Agency** (Canada)—This government organization is responsible for safeguarding food in Canada and performs foresight exercises on a semiregular basis.[9]
- **Centre for Environmental Risks and Futures, Cranfield University** (United Kingdom)—Founded in January 2011, this academic group conducts regular research into foresight methodologies and has been contracted in the past by the UK government to carry out relevant horizon scans.[10]
- **Horizon Scanning and Futures Team, Department of Environment, Food and Rural Affairs** (United Kingdom)—"A leader in horizon scanning work at a global level, this group provides policy advice, identifies future risks and opportunities, and topic specific workshops."[11]
- **European Food Safety Authority** (EU)—This organization is responsible for a wide range of food safety issues in the European Union and carries out assessments of emerging risks that utilize aspects of foresight methodologies.[12]
- **Food Standards Agency** (United Kingdom)—This is the government agency in the United Kingdom responsible for food safety and hygiene, and it has been exploring the use of foresight methodologies in the area of food safety.[13]
- **Strategic Foresight, Department of Agriculture, Fisheries and Forestry** (Australia)—Focused on environmental scanning and foresight techniques to identify future issues, this government organization works with local and international partners, and its work includes food safety.[14]

[9]See http://www.inspection.gc.ca/about-the-cfia/strategic-priorities/cfia-s-strategic-priorities/eng/1521141282459/1521141282849.

[10]See https://theriskexchange.wordpress.com.

[11]See https://webarchive.nationalarchives.gov.uk/20070506093923/http://horizonscanning.defra.gov.uk.

[12]See http://www.efsa.europa.eu/en/efsajournal/pub/5359.

[13]See http://www.operational-research.gov.uk/recruitment/departments/fsa.

[14]See http://www.agriculture.gov.au/animal/health/strategy.

Example of Combining Separate Horizon Scans

The United Kingdom's Futures Toolkit includes case studies of how seven different government agencies and ministries make use of futuring tools. Each case study sets out the purpose of the work, the tools used, resources required, the work's sponsor, specific outputs, particular successes, and challenges. Five of these agencies—the Environment Agency, the Forestry Commission England, the Health and Safety Executive, Revenues and Customs, and Natural England—make specific mention of the purpose of their horizon-scanning work (UK Government Office for Science, 2017). The purposes cited differ and include using horizon scanning to identify new and emerging issues and trends; improve the evidence base for decision making and risk mitigation; help identify risks and opportunities; integrate externalities into business planning; and inform strategy, provoke discussion, and shape thinking.

LESSONS LEARNED FROM HORIZON SCANNING

In addition to lessons identified during the webinar held by the committee, several key actors, including the National Intelligence Council (NIC, 2017), the U.S. Forest Service (Hines et al., 2018), the UK government (Carney, 2018), and the European Union (European Commission, 2015), have distilled lessons from their past use of horizon scanning.

National Intelligence Council Global Trends Report

Improvements in methodology integrated into the most recent iteration of the Global Trends report produced by the National Intelligence Council include (NIC, 2017)

- involving as many experts as possible from a broad range of countries and with a wide variety of backgrounds;
- exploring regional trends first and then aggregating them to create a global picture;
- avoiding connecting conclusions to specific dates, but rather focusing on timeframes relevant to policy making—near-term (5-year), focused on issues confronting the next U.S. administration, and long-term (20-year), to support U.S. strategic planning;
- placing greater focus on difficult-to-measure social and cultural factors that could influence the future events;
- making increased use of analytic simulations, "employing teams of experts to represent key international actors—to explore the future trajectories for regions of the world, the international order, the security environment, and the global economy"; and

- integrating "the potential for discontinuities in all regions and topic areas, developing an appreciation for the types of discontinuities likely to represent fundamental shifts from the status quo."

U.S. Forest Service

Also in the United States, efforts to establish a horizon-scanning system in the Forest Service led to a number of key reflections, including the following (Hines et al., 2018):

- **Background information versus horizon scanning**—In general, as horizon scanning is focused on what might happen in the future, the information used in scans should be new (from within the past few years). Older sources may still be useful as background information but not seen as part of an emerging trend.
- **New to me versus new to the world**—Some information may appear new but be familiar to those well versed in the field. This observation highlights the importance of including subject-matter experts on the issues being scanned.
- **How to handle "coaching" of volunteers**—Having those undertaking the scans start from the same place and (to the extent possible) use complementary approaches is important. Regular interactions with those undertaking the scans are also important to reinforce guidance provided to them, as is approaching feedback in a positive, constructive manner (as opposed to criticizing participants).
- **Focusing on outside issues**—Policy makers and decision makers are often well versed in emerging issues in their own field. Participants in horizon scanning can add particular value by looking at events or trends from outside the core field (in this case the bioeconomy) that could also have an impact.
- **Staying connected**—Whether or not the trend or event identified comes from the core field, its implications for the core field must be clearly articulated. This can be achieved by specifically tasking those undertaking the scan to explicitly address the implications for the core field.
- **Stretching into the future**—It is important to encourage those undertaking the scan to think further into the future. One approach is asking them to "tag" the scan to one of the three horizons identified earlier in Figure Annex 6-1.
- **Tagging discipline**—As the number of scans grows, it becomes more difficult to track their content and how they relate to each

other and the issue being investigated. It is important to add tags, keywords, or relationship indicators to the scans to facilitate their ongoing use.

- **Current issues**—As discussed above, those familiar with a field (be they technical experts or policy makers) are often aware of current emerging issues. Frequently, these issues are not well articulated or documented. It will greatly improve the utility of scans and increase the value of engaging generalists or specialists from other fields if an effort is made early in the process to map current emerging issues and provide this information to all those involved in the horizon-scanning process.

UK Government

Based on the use of horizon scanning in the UK government, 10 key rules have been identified. Some of these rules have been discussed in this annex and in the main text of Chapter 6—for example, (1) that horizon scanning is not about predicting the future but about challenging assumptions and increasing options, (2) that there is a lack of common understanding about what horizon scanning is or the terms being used, and (3) that focusing on impact and explicitly exploring the implications of the trends or events identified are important. Other rules bear emphasizing here, such as the importance of (Carney, 2018)

- asking the unasked questions (or attempting to explore the unknown unknowns), as opposed to focusing on something that is already known or a specific desirable outcome;
- having a champion or dedicated client for the process—someone that wants the results and is keen and willing to integrate and act upon the results; and
- involving generalists (or at least participants from outside the commissioning domain) and understanding their value in identifying the unasked questions or implications not seen to date, as well as in presenting the outcome of the work.

European Union

Similarly, the European Union has identified a number of key considerations, including (European Commission, 2015)

- having a clear organizational structure (or institutional support) for horizon scanning, such as arrangements for coordination and brokerage with users;

- developing a specific implementation plan to take advantage of the scanning results, or integrating the scan into a more comprehensive foresight process;
- undertaking both continuous horizon-scanning processes in strategically important areas and stand-alone projects designed to answer explicit questions;
- using expert review to help transform information into actionable knowledge;
- tailoring the approach used and people involved to the scan's end goal, recognizing that processes for understanding a new policy environment will be different from those for considering the implications of emerging trends and new events;
- involving the end user/client of a horizon scan (such as policy makers) in the planning stages, such as the initial sense-making activities; and
- ensuring that the results of the scan are accessible to the eventual end user, likely necessitating that they be "translated" at a suitable stage.

ADDITIONAL TOOLS FOR FUTURE THINKING

Superforecasting

As discussed briefly in the main text of Chapter 6, in 2010, the Intelligence Advanced Research Projects Agency (IARPA) created a program to explore how crowdsourcing can improve forecasting[15]:

> Generally, forecasts are prepared using expert judgment by individuals and small groups. Empirical research outside the intelligence community has shown that the accuracy of judgment-based forecasts is consistently improved by mathematically aggregating many independent judgments. The goal of the ACE Program is to dramatically enhance the accuracy, precision, and timeliness of forecasts for a broad range of event types, through the development of advanced techniques that elicit, weight, and combine the judgments of many intelligence analysts.

Similar programs have subsequently focused on developing "innovative solutions and methods for integrating crowd sourced forecasts and other data into accurate, timely forecasts on worldwide issues."[16] There have

[15]See IARPA, Aggregative Contingent Estimation: https://www.iarpa.gov/index.php/research-programs/ace/baa.

[16]See IARPA, Geopolitical Forecasting Challenge: https://www.iarpa.gov/challenges/gfchallenge.html.

also been programs created "to develop and test methods for generating accurate forecasts for significant science and technology (S&T) milestones, by combining the judgments of many experts"[17]; and "to develop automated methods that aid in the systematic, continuous, and comprehensive assessment of technical emergence using information found in published scientific, technical, and patent literature."[18]

IARPA tested the tools for aggregating crowdsourced forecasting in a 4-year series of tournaments, where

> contestants competed to produce the most accurate predictions on a wide array of geopolitical and economic topics, ranging from the performance of financial markets, to the risk of Greece leaving the Eurozone, to the prospects of a violent Sino-Japanese clash in the East China Sea. (Tetlock et al., 2017)

One successful team subsequently identified a number of key findings (Tetlock et al., 2017):

- "Some methods for extracting wisdom from crowds are better than others. Prediction polls yield a probabilistic forecast by aggregating the predictions of individuals…. In contrast, prediction markets rely on forecasters buying and selling contracts whose ultimate value depends on the outcome of a future event."
- "The winning algorithm across all tournament years was a log-odds weighted-averaging equation that extremized median probability judgments … as a function of the diversity of the views feeding into the median."
- "Some forecasters are, surprisingly consistently, better than others."
- "Learning—and therefore improvement—is possible, even though the world of international politics and economics … is not learning-friendly."

The last two of these findings form the basis of superforecasting (Tetlock and Gardner, 2015). This process brings together in teams those individuals with a proven track record of being able to make more accurate predictions, supported by specialized tools and algorithms so as to further increase their accuracy.

[17]IARPA, Forecasting Science & Technology: https://www.iarpa.gov/index.php/research-programs/forest.

[18]IARPA, Foresight and Understanding from Scientific Exposition: https://www.iarpa.gov/index.php/research-programs/fuse.

A thorough assessment of the performance of superforecasters during the tournaments demonstrated that they were significantly more accurate in making predictions than other participants and that "tight restrictions on time and information did not erode the superforecaster advantage." They were also better able to differentiate between signal and noise and were the fastest learners in the tournament. These studies demonstrated that while certain types of people are more likely to become superforecasters, certain skills and organizational arrangements can increase the ability to make accurate predictions. Thus, "superforecasters are partly discovered and partly created." Mellers and colleagues (2015) identify "four mutually reinforcing explanations of superforecaster performance: (a) cognitive abilities and styles, (b) task-specific skills, (c) motivation and commitment, and (d) enriched environments."

The first cohorts of superforecasters were identified during the IARPA forecasting tournaments. Efforts to identify and recruit additional individuals have continued through Good Judgment Open.[19] Since the tournaments, the approach has been developed into a commercial service through Good Judgment, which works with governments, the financial sector, and civil society and nongovernmental organizations, providing forecasting, training services, and tools and techniques.[20]

UK Government Office for Science's Futures Toolkit

In 2017, the UK Government Office for Science (GO-Science) published a Futures Toolkit that "policy professionals can use to embed long term strategic thinking in the policy and strategy process." It is intended to be "practical rather than theoretical and … based on GO-Science's own experience of running futures work and has been developed in collaboration with other government departments and futures practitioners who use these tools regularly in a wide range of settings" (UK Government Office for Science, 2017). The tools in the kit are structured around four common uses for foresight:

- gathering intelligence about the future,
- exploring the dynamics of change,
- describing what the future may be like, and
- developing and testing policy and strategy.

As the task assigned to this committee was to "develop ideas for horizon scanning mechanisms to identify new technologies, markets, and data

[19]See https://www.gjopen.com.
[20]See https://goodjudgment.com.

sources that have the potential to drive future development of the bioeconomy," our focus was on the use of foresight tools to gather bioeconomy-related intelligence about the future.

The toolkit describes four tools relevant for gathering intelligence about the future (UK Government Office for Science, 2017):

- **Horizon scanning**—as described in this chapter.
- **7 Questions**—This is "an interview technique for gathering the strategic insights of a range of internal and external stakeholders." It can be used to identify conflicting or challenging views of the future, extract deep information about underlying concerns in a policy area, and stimulate individuals' thinking in preparation for a futures workshop. It is a fairly quick process, with each interview taking about an hour to conduct and another hour to write up.
- **The issues paper**—This paper "presents quotes from the 7 Questions interviews to illustrate the strategic issues and choices around the policy and strategy agenda." It can be used to capture different perspectives from those captured by the 7 Questions interviews about what success in the future will be like and what needs to be done to achieve it. This is another quick process, taking around 30 minutes to process each of the seven questions per interview.
- **Delphi process**—This is "a consultation process used to gather opinion from a wide group of subject experts about the future and to prioritize the issues of strategic importance." It can be used to gather opinion from a group of experts, refine thinking on the future, and highlight the potential trade-offs and choices that policy design will need to address. It is a more time-consuming process that can take several weeks.

The tools in the kit are then combined in different ways to meet different needs, as captured in a series of pathways (UK Government Office for Science, 2017):

- "Pathway 1—exploring underlying issues or causes when scoping or defining a policy area;
- Pathway 2—determining a vision for a new policy area;
- Pathway 3—testing policy options for an existing policy area under time constraints;
- Pathway 4—testing policy options for a new policy area;
- Pathway 5—exploring and communicating the complexity of a situation;

- Pathway 6—identifying futures research and evidence priorities; and
- Pathway 7—identifying and prioritizing future opportunities and threats for action."

Given the focus of this study and the committee's Statement of Task, Pathways 6 and 7 are of particular relevance. These pathways use additional tools, including (UK Government Office for Science, 2017) the following:

- **Driver mapping** is used to "identify drivers shaping the future, identify which drivers are most important for the future of the policy area or strategic endeavor, and distinguish between certain and uncertain outcomes resulting from the action of drivers." It is another quick tool, usually taking 1–2 hours depending on whether it is accomplished in small groups or as a workshop.
- **Roadmapping** "shows how a range of inputs—research, trends, policy interventions, for example—will combine over time to shape future development of the policy or strategy area of interest." It can be used to "build a holistic picture of the different elements in a project and how they combine over time" and "deepen understanding of the connections and relationships between different elements." This tool need not take a long time, and an initial version can be assembled in about 1.5 hours. It can be revisited and improved throughout the life of a foresight program.
- **SWOT analysis** examines "Strengths, Weaknesses, Opportunities, and Threats. Strengths and Weaknesses [which] are internal factors that need to be taken account of when developing policy or strategy. Opportunities and Threats are external factors that need to be considered." The analysis can identify what needs to be done to capture and build on opportunities, what needs to be done to mitigate threats, and internal priorities and challenges. A simple SWOT analysis can be accomplished in 1 hour.

Pathway 6, "identifying futures research and evidence priorities," begins with horizon scanning but feeds the results into 7 Questions, issues papers, driver mapping, and then roadmapping. Pathway 7, "identifying and prioritizing future opportunities and threats for action," also starts with horizon scanning but feeds the results into driver mapping and SWOT analysis.

REFERENCES

Amanatidou, E., M. Butter, V. Carabias, T. Könnölä, M. Leis, O. Saritas, P. Schaper-Rinkel, and V. van Rij. 2012. On concepts and methods in horizon scanning: Lessons from initiating policy dialogues on emerging issues. *Science and Public Policy* 39(2):208–221. doi: 10.1093/scipol/scs017.

Bracken, P. 2006. Net assessment: A practical guide. *Parameters* 36(1):90–100. https://www.comw.org/qdr/fulltext/06bracken.pdf (accessed September 4, 2019).

Brown, I. T., A. Smale, A. Verma, and S. Momandwall. 2005. Medical technology horizon scanning. *Australasian Physical & Engineering Sciences in Medicine* 28(3). https://link.springer.com/article/10.1007/BF03178717 (accessed September 4, 2019).

Brown, M. J., L. V. Dicks, R. J. Paxton, K. C. Baldock, A. B. Barron, M. P. Chauzat, B. M. Freitas, D. Goulson, S. Jepsen, C. Kremen, J. Li, P. Neumann, D. E. Pattemore, S. G. Potts, O. Schweiger, C. L. Seymour, and J. C. Stout. 2016. A horizon scan of future threats and opportunities for pollinators and pollination. *PeerJ* 4:e2249. doi: 10.7717/peerj.2249.

CADTH (Canadian Agency for Drugs and Technologies in Health). 2015. *Horizon scanning process.* https://www.cadth.ca/sites/default/files/externalprocesses_horizonscanning program.pdf (accessed September 4, 2019).

Carney, J. 2018. The ten commandments of horizon scanning. *Futures, foresight and horizon scanning*. https://foresightprojects.blog.gov.uk/2018/03/08/the-ten-commandments-of-horizon-scanning (accessed September 4, 2019).

Chong, T. K., J. K. Y. Hann, J. T. T. Hua, W. R. Fah, S. A. Lim, and C. C. Seng. 2007. *Risk Assessment and Horizon Scanning Experimentation Centre*. https://www.dsta.gov.sg/docs/default-source/dsta-about/risk-assessment-and-horizon-scanning-experimentation-centre.pdf?sfvrsn=2 (accessed September 4, 2019).

Cyranoski, D., and H. Ledford. 2018. *Genome-edited baby claim provokes international outcry.* https://www.nature.com/articles/d41586-018-07545-0 (accessed September 4, 2019).

Doos, L., C. Packer, D. Ward, S. Simpson, and A. Stevens. 2016. Past speculations of the future: A review of the methods used for forecasting emerging health technologies. *BMJ Open* 6(3):e010479. doi: 10.1136/bmjopen-2015-010479.

Douw, K., H. Vondeling, D. Eskildsen, and S. Simpson. 2003. Use of the Internet in scanning the horizon for new and emerging health technologies: A survey of agencies involved in horizon scanning. *Journal of Medical Internet Research* 5(1):e6. doi: 10.2196/jmir.5.1.e6.

EBRC (Engineering Biology Research Consortium). 2019. *Engineering biology: A research roadmap for the next generation bioeconomy*. https://roadmap.ebrc.org (accessed October 15, 2019).

European Commission. 2015. *Models of horizon scanning: How to integrate horizon scanning into European research and innovation policies*. http://publications.europa.eu/resource/cellar/88ea0daa-0c3c-11e6-ba9a-01aa75ed71a1.0001.01/DOC_1 (accessed September 4, 2019).

European Environmental Agency. 2011. *Annex 6—Netherlands country case study.* https://www.eea.europa.eu/publications/blossom/annex-6-2014-netherlands-country (accessed October 15, 2019).

FAO (Food and Agriculture Organization of the United Nations). 2013. *Horizon scanning and foresight: An overview of approaches and possible applications in food safety*. http://www.fao.org/3/a-i4061e.pdf (accessed September 4, 2019).

Frank, A. B. 2016. Toward computational net assessment. *Journal of Defense Modeling and Simulation: Applications, Methodology, Technology* 14(1):79–94. doi: 10.1177/1548512916681672.

Habegger, B. 2009. *Horizon scanning in government concept, country experiences, and models for Switzerland*. Zurich, Switzerland: Center for Security Studies ETH Zurich. https://works.bepress.com/beathabegger/16 (accessed September 4, 2019).

HealthPACT (Health Policy Advisory Committee on Technology). 2011. *Welcome to the Australia and New Zealand Horizon Scanning Network (ANZHSN)*. http://www.horizonscanning.gov.au (accessed October 15, 2019).

Hines, A., D. N. Bengston, M. J. Dockry, and A. Cowart. 2018. Setting up a horizon scanning system: A U.S. federal agency example. *World Futures Review* 10(2):136–151. https://www.fs.fed.us/nrs/pubs/jrnl/2018/nrs_2018_hines-a_001.pdf (accessed September 4, 2019).

Horton, A. 1999. A simple guide to successful foresight. *Foresight* 1(1):5–9.

IRM (Institute for Risk Management). 2018. *Horizon scanning: A practitioner's guide*. https://www.theirm.org/media/4047721/Horizon-scanning_final2.pdf (accessed September 4, 2019).

Konecny, A. D. 1988. *Net assessment: An examination of the process*. Thesis. Naval Postgraduate School, Monterey, California. https://apps.dtic.mil/dtic/tr/fulltext/u2/a205104.pdf (accessed October 15, 2019).

Lentzos, F., and J. Littlewood. 2018. DARPA's Prepare program: Preparing for what? *Bulletin of the Atomic Scientists*. https://thebulletin.org/2018/07/darpas-prepare-program-preparing-for-what (accessed September 4, 2019).

Mehand, M. S., P. Millett, F. Al-Shorbaji, C. Roth, M. P. Kieny, and B. Murgue. 2018. World Health Organization methodology to prioritize emerging infectious diseases in need of research and development. *Emerging Infectious Diseases* 24(9). https://wwwnc.cdc.gov/eid/article/24/9/17-1427_article (accessed September 4, 2019).

Mellers, B., E. Stone, T. Murray, A. Minster, N. Rohrbaugh, M. Bishop, E. Chen, J. Baker, Y. Hou, M. Horowitz, L. Ungar, and P. Tetlock. 2015. Identifying and cultivating superforecasters as a method of improving probabilistic predictions. *Perspectives on Psychological Science* 10(3):267–281. doi: 10.1177/1745691615577794.

Miles, I., and O. Saritas. 2012. The depth of the horizon: Searching, scanning and widening horizons. *Foresight* 14(6):530–545. doi:10.1108/14636681211284953.

NIC (National Intelligence Council). 2017. Methodological note. In *Global trends: Paradox of progress*. https://www.dni.gov/index.php/global-trends/methodological-note (accessed September 4, 2019).

OECD (Organisation for Economic Co-operation and Development). n.d.a. *Overview of methodologies, futures thinking in brief, future schooling*. https://www.oecd.org/site/schoolingfortomorrowknowledgebase/futuresthinking/overviewofmethodologies.htm (accessed September 4, 2019).

OECD. n.d.b. *Futures thinking in brief, future schooling*. https://www.oecd.org/site/schoolingfortomorrowknowledgebase/futuresthinking/futuresthinkinginbrief.htm (accessed September 4, 2019).

Office of Technical Intelligence. 2015. *Technical assessment: Data enabled technology watch and horizon scanning*. https://apps.dtic.mil/dtic/tr/fulltext/u2/1010211.pdf (accessed September 4, 2019).

O'Malley, S. P., and E. Jordan. 2009. Horizon scanning of new and emerging medical technology in Australia: Its relevance to Medical Services Advisory Committee health technology assessments and public funding. *International Journal of Technology Assessment in Health Care* 25(3):374–382. doi: 10.1017/S0266462309990031.

Popper, R. 2008. Foresight methodology. In *The handbook of technology foresight: Concepts and practice*, edited by L. Georghio, J. Cassingena Harper, M. Keenan, I. Miles, and R. Popper. Cheltenham, UK: Edward Elgar.

Rowe, E., G. Wright, and J. Derbyshire. 2017. Enhancing horizon scanning by utilizing pre-developed scenarios: Analysis of current practice and specification of a process improvement to aid the identification of important "weak signals." *Technological Forecasting and Social Change* 125:224–235. https://www.sciencedirect.com/science/article/pii/S0040162517300707 (accessed September 14, 2019).

Schultz, W. L. 2006. The cultural contradictions of managing change: Using horizon scanning in an evidence-based policy context. *Foresight* 8(4):3–12.

Smith, J., A. Cook, and C. Packer. 2010. Evaluation criteria to assess the value of identification sources for horizon scanning. *International Journal of Technology Assessment in Health Care* 26(3):348–353. doi: 10.1017/S026646231000036X.

Stevens, A., R. Milne, R. Lilford, and J. Gabbay. 1999. Keeping pace with new technologies: Systems needed to identify and evaluate them. *British Medical Journal* 319(7220):1291. doi: 10.1136/bmj.319.7220.1291.

Sutherland, W. J., H. Ilary, A. Llison, R. Osalind, A. Veling, I. P. Bainbridge, L. Bnnun, D. J. Bullock, A. Clements, H. Q. P. Crick, D. W. Gibbons , S. Smith, M. R. W. Rands, P. Rose, J. P. W. Scharlemann, and M. S. Warren. 2012. Enhancing the value of horizon scanning through collaborative review. *Oryz* 45(3):368–374. https://doi.org/10.1017/S0030605311001724 (accessed September 4, 2019).

Sutherland, W. J., S. Broad, S. H. M Butchart, S. J. Clarke, A. M. Collins, L.V. Dicks, H. Doran, N. Esmail, E. Fleishman, N. Frost, K. J. Gaston, D. W. Gibbons, A. C. Hughes, Z. Jiang, R. Kelman, B. LeAnstey, X. le Roux, F. A. Lickorish, K. A. Monk, D. Mortimer, J. W. Pearce-Higgins, L. S. Peck, N. Pettorelli, J. Pretty, C. L. Seymour, M. D. Spalding, J. Wentworth, and N. Ockendon. 2019. A horizon scan of emerging issues for global conservation in 2019. *Trends in Ecology & Evolution* 34(1):83–94.

Tetlock, P. E., and D. Gardner. 2015. *Superforecasting: The art and science of prediction*. New York: Crown.

Tetlock, P. E., B. A. Mellers, and J. P. Scoblic. 2017. Bringing probability judgments into policy debates via forecasting tournaments. *Science* 355(6324):481–483. doi: 10.1126/science.aal3147.

UK (United Kingdom) Government Cabinet Office. 2013. *Review of cross-government horizon scanning*. https://www.gov.uk/government/publications/review-of-cross-government-horizon-scanning (accessed September 4, 2019).

UK Government Office for Science. 2013. *Horizon Scanning Programme: A new approach for policy making.* https://www.gov.uk/government/news/horizon-scanning-programme-a-new-approach-for-policy-making (accessed September 4, 2019).

UK Government Office for Science. 2017. *The futures toolkit: Tools for futures thinking and foresight across U.K. government.* https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/674209/futures-toolkit-edition-1.pdf (accessed September 4, 2019).

Wellcome Trust. 2017. *Report from the December 2017 gene drive sponsors and supporters' forum.* https://wellcome.ac.uk/sites/default/files/gene-drive-forum-notes-dec17.pdf (accessed October 15, 2019).

WHO (World Health Organization). 2017. *Methodology for prioritizing severe emerging diseases for research and development.* https://www.who.int/blueprint/priority-diseases/RDBlueprint-PrioritizationTool.pdf (accessed September 4, 2019).

Wintle, B. C., C. R. Boehm, C. Rhodes, J. C. Molloy, P. Millett, L. Adam, R. Breitling, R. Carlson, R. Casagrande, M. Dando, R. Doubleday, E. Drexler, B. Edwards, T. Ellis, N. G. Evans, R. Hammond, J. Haseloff, L. Kahl, T. Kuiken, B. R. Lichman, C. A. Matthewman, J. A. Napier, S. S. ÓhÉigeartaigh, N. J. Patron, E. Perello, P. Shapira, J. Tait, E. Takano, and W. J. Sutherland 2017. A transatlantic perspective on 20 emerging issues in biological engineering. *eLIFE*, November 14. https://elifesciences.org/articles/30247 (accessed September 4, 2019).

PART III

UNDERSTANDING THE RISKS ASSOCIATED WITH THE U.S. BIOECONOMY

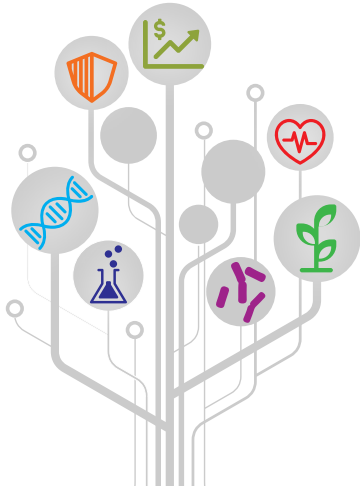
The previous two parts of this report describe the components of the bioeconomy, the ecosystem in which the bioeconomy operates, and articulate its economic importance. This holistic examination enabled the committee to identify risks related to the bioeconomy and potential policy options for addressing those risks. This discussion responds directly to elements of the committee's Statement of Task and a major motivating factor for the commissioning of this study.

Chapter 7 reviews the risks identified by the committee that pertain to the U.S. bioeconomy. These risks are divided into two major categories: those related to *failing to promote the U.S. bioeconomy* (risks resulting from actions or inactions that could prevent the bioeconomy from flourishing), and those resulting from *a failure to protect the U.S. bioeconomy* (risks to the bioeconomy and risks posed by its subversion or misuse). The discussion also addresses policy tools that could be used to mitigate the identified risks, and considers the implications of such measures.

While it is impossible to imagine the absence of a U.S. bioeconomy, should the U.S. bioeconomy not reach its potential, the benefits it might otherwise have delivered would be forfeit. These benefits might include safer and improved foods, advanced materials, sources of clean energy, pharmaceuticals and improved health, a cleaner and lower-carbon-emission environment, jobs, and economic growth—all of which would either be foregone or require importation from economic competitors overseas. In the latter case, U.S. consumers might still benefit, but U.S. producers

would lose "first mover advantages" and leadership in the relevant technologies. These risks are addressed in Chapter 7 with respect to certain aspects of the bioeconomy, but they are not explicitly quantified or analyzed in depth; they represent the cost to the United States of not realizing—or not realizing first—the various benefits sought from the bioeconomy that have been discussed elsewhere in this report.

This chapter sets the stage for the final part of the report, in which the committee provides its overall conclusions and recommendations.



7

ECONOMIC AND NATIONAL SECURITY RISKS PERTAINING TO THE BIOECONOMY

Summary of Key Findings

- Failure to promote the U.S. bioeconomy domestically has the potential to diminish U.S. scientific leadership in the global bioeconomy. Identified risks include
  - — insufficient funding for research and development,
  - — asymmetric research constraints,
  - — an inadequate workforce, and
  - — an ineffective or inefficient intellectual property and regulatory environment.
- Failure to protect the U.S. bioeconomy from intentional acts that could harm or misuse it has the potential to hinder the continued progress of the U.S. bioeconomy, as well as to facilitate harm to society at large. Identified risks include
  - — constrained access to international data,
  - — use of bioeconomy datasets to the detriment of individual privacy or national security,
  - — cyber risks associated with the bioeconomy,

  - economic attack through theft and infiltration,
  - inappropriate state involvement in business activities,
  - trade barriers,
  - critical infrastructure vulnerabilities, and
  - traditional biosecurity vulnerabilities.
- There is an unusually high level of legal uncertainty for companies about patent eligibility for technologies relevant to the bioeconomy.
- The growing bioeconomy's reliance on software, networking, and computer hardware tools makes it vulnerable to fundamental cybersecurity risks similar to those faced by other sectors. In particular, bioeconomy stakeholders are at high risk for cyber intrusions, cyber-enabled data loss or manipulation, and intellectual property theft as the risks and potential adverse biological outcomes are not well understood by the community.
  - Improving the sharing of information on cyberthreats has the potential to help members of the bioeconomy reduce the risk of cyber intrusion, manipulation, or disruption as it has for other sectors.
  - Software developers active within the bioeconomy—similar to developers in other domains—tend not to have the training or knowledge to develop secure source code.

As described in Chapter 3, the bioeconomy represents an important and growing share of the U.S. economy. The committee believes the bioeconomy's importance will continue to grow as biotechnology makes greater inroads in pharmaceutical production and the delivery of health care, in agriculture, in the generation of energy, in the manufacture of specialty chemicals and materials, and in the production of other goods and services, particularly as biological production processes displace conventional chemical processes. The bioeconomy is also important to national defense—not only in the narrow sense of countering biological weapons but also for a broader range of defense needs (DiEuliis, 2018), including military medicine (NRC, 2004); sensors, electronics, computing, materials, logistics, and soldier health and performance (Armstrong et al., 2010; NRC, 2001; Tucker, 2019); and energy (NRC, 2012). In these defense-related applications, biotechnology is a thoroughly dual-use[1]

[1]The term "dual-use" has two related but distinct meanings. With respect to export controls, it refers to items produced for commercial markets that can also be used in military systems, and that therefore are subject to national security export controls. With respect to scientific research, the term also refers to legitimate scientific developments that can be misused for harm. Biotechnology is dual-use in both respects, recognizing that there are military uses that do not involve the development and production of biological weapons, which is banned by the international Biological Weapons Convention.

technology, meaning that the same science and technology base underlies both military and commercial applications, making it difficult to distinguish the economic security and national security aspects of the technology. This ambiguity is exacerbated by the continued emergence and evolution of new biotechnologies whose ultimate applications and significance for the economy or for national security may not yet be clear. Even if the economic or national security impact of specific technologies could be determined unambiguously, these two areas are interrelated in that a country's economic vitality affects its ability to support its national defense and other national needs. Moreover, a nation that is unable to support an economically vital industrial sector is potentially vulnerable to coercion or monopoly pricing from foreign suppliers. Given this blurring of economic and national security concerns, much of this chapter's discussion does not differentiate economic from national security risks.

The first section of the chapter addresses potential harms to the health and competitiveness of the U.S. bioeconomy from failure to sufficiently provide the attributes, resources, and environment that are necessary to allow it to flourish—*failure to promote* the bioeconomy. The second section addresses *failure to protect* the bioeconomy from intentional acts that could harm it, such as theft of intellectual property (IP) or datasets, conferring a competitive advantage on the recipients of that illicitly gained information. It also addresses *failure to protect from harms mediated by the bioeconomy* that relate to its subversion or misuse, including such traditional biosecurity risks as the development of biological weapons agents, as well as means by which attackers could hijack entities within the bioeconomy to pose risks to people, agriculture, and the environment or to threaten U.S. national and economic security more generally. It is important to note that the committee did not prioritize or rank the risks identified in this chapter, and that while the committee strove to be as comprehensive as possible in outlining risks to the bioeconomy, this chapter should not be taken as providing a comprehensive list. Moreover, as discussed in the introduction to Part III, although this chapter addresses risks associated with the failure of certain aspects of the bioeconomy, that could leave the United States vulnerable to coercion or monopoly pricing from foreign suppliers, it does not quantify or analyze these risks in depth. In the latter case, U.S. consumers might still benefit, but U.S. producers would lose "first mover advantages" and leadership in the relevant technologies. The chapter ends with conclusions.

FAILURE TO PROMOTE THE BIOECONOMY

Risks related to failure to promote the bioeconomy include insufficient U.S. government research and development (R&D) investment, asymmetric research constraints, an inadequate workforce, an ineffective

or inefficient IP environment, and an ineffective or inefficient regulatory environment.

Insufficient U.S. Government Research and Development Investment

As explored in Chapters 3, 4, and 5, a history of strong and sustained U.S. government investment in the life sciences, in computing and information sciences, and in engineering has powered the development of today's world-leading bioeconomy. To retain this world leadership position, the United States will need to sustain its investment in basic research and the development of supporting and enabling technologies. The committee identified the potential risks described below should U.S. investment in R&D be insufficient.

Loss of Scientific Leadership

Insufficient support for fundamental research, whether from the U.S. government or from major nongovernmental funders, will erode the United States' ability to achieve breakthrough scientific results, as well as the type of incremental learning that can also have direct economic application. In the longer run, insufficient research support will erode the United States' ability to develop and recruit the world's best research talent, including domestic talent, particularly in competition with other countries that are investing heavily in their own bioeconomies (as discussed in Chapter 4). Specifically, loss of U.S. scientific leadership could have the following consequences:

- Significant developments that drive innovation and economic returns could increasingly happen outside the United States.
- Students and researchers who seek the opportunity to work with the world's best researchers could leave or be less likely to come to the United States, depriving the nation of their expertise.
- Start-ups and other corporations that are formed to build on the scientific advances realized through R&D and that are staffed by the researchers, students, and technologists who have worked with influential academic research groups could be less likely to thrive within the United States. Although research results that are published in the open literature are available anywhere in the world, the existence of biotech innovation clusters, such as those in the San Francisco Bay and Boston areas, shows that there is value to founding a biotech company close to major research institutions and in the vicinity of other biotech firms (Audretsch and Feldman, 1996; Bailey and Montalbano, 2017; Feldman and

Massard, 2002; NASEM, 2017b). Proximity to scientific leaders matters, as does the rapid transfer of tacit knowledge and learning from peers and competitors.

- U.S. researchers and institutions could be less able to participate in the establishment of global norms, practices, and ethical standards that reflect U.S. values.

Insufficient Development of Enabling Tools, Technologies, and Standards

Investments in basic research have historically led to new applications, even more so when the research has led to the development of a tool or technology that spurred greater innovation in related applications, as has been the case for enabling technologies such as DNA sequencing, DNA synthesis, genome-editing tools, high-performance computing, and data-sharing platforms. Continued funding and support for research that could extend and improve these tools or result in a new enabling technology is paramount to maintaining scientific leadership; however, identifying what research to fund is a perennial challenge. Within the synthetic biology community, the Engineering Biology Research Consortium (EBRC), a nonprofit public–private partnership dedicated to advancing the engineering of biology, has developed a technology roadmap to identify priority areas of precompetitive research over the next two decades (EBRC, 2019). This roadmap, and others like it, can be used by U.S. government programs to focus their investments on precompetitive research topics that will accelerate large segments of the field as a whole. The EBRC roadmap focuses on four technical areas—engineering DNA, biomolecular engineering, host engineering, and data science—highlighting the potential of technical developments in these domains to enable rapid advances across a number of application sectors, including food and agriculture, health and medicine, energy, industrial biotechnology, and environmental biotechnology.

It is worth noting that data-sharing capabilities have greatly accelerated various scientific discoveries and their downstream applications, as is discussed in Chapter 5. Insufficient support for these efforts has the potential to constrain access to data on which researchers within the U.S. bioeconomy rely and could hamper future efforts to share and combine large datasets more efficiently (Toga and Dinov, 2015).

In addition to supporting fundamental scientific research, U.S. government investments and institutions, such as the National Institute of Standards and Technology, support the development of measurement techniques and standards that may not be profitable for any individual private firm to develop but that benefit the U.S. bioeconomy as a whole by making many U.S. firms more productive. For example, the development

and adoption of a set of standard biological components with reproducible characteristics has the potential to enable interoperability, longer and more complex supply chains, and the generation of more complex products (Galdzicki et al., 2011). The number of registries and databases aiming to catalog and make available standard components is growing.[2] Insufficient attention to and investment in these underlying technologies, particularly in the face of competition from other nations whose governments are funding such investment, will make the U.S. bioeconomy less competitive.

Asymmetric Research Constraints

Constraints placed on U.S. bioeconomy research laboratories but not on academic competitors overseas can create a competitive disadvantage, whether by limiting or preventing U.S. researchers from conducting certain types of research, limiting access to particular materials or samples, or providing incentives for productive researchers to leave the United States for countries with less stringent regulatory environments.

For example, human embryonic stem cells (hESCs) are currently being used in a number of clinical studies, including those focused on macular degeneration of the retina, diabetes, heart repair, and the induction of T cell–mediated immunity. In the United Kingdom, the Human Fertilization and Embryology Act of 1990 and the Human Reproductive Cloning Act of 2001 permit the destruction of embryos to obtain hESCs for research and treatment of serious diseases (Dhar and Ho, 2009). As a result, the United Kingdom now has a global leadership position in the development of clinical-grade lines suitable for regenerative therapies. In contrast, the U.S. regulatory landscape has been much more restrictive than that of not only the United Kingdom but also, for example, Japan and Singapore (Dhar and Ho, 2009). Following an outright ban in 1995 on the destruction of human embryos for research, the restrictions were relaxed in 2009 to allow the generation of new human embryonic cell lines, with a number of ethical provisions involving donor consent.[3] More than 100 lines in the National Institutes of Health (NIH) hESC registry that carry specific mutations linked to monogenic diseases, such as cystic fibrosis and Huntington's disease, were generated but not widely utilized for research because of ethical issues, the limited number of diseases involved, and the regulatory landscape (Ilic and Ogilvie, 2017). An analysis of the research literature shows that the U.S.-based share of worldwide research into

[2]iGEM Registry of Standard Biological Parts (http://parts.igem.org/Main_Page); the Synthetic Biology Open Language (http://sbolstandard.org and https://doi.org/10.1016/j.synbio.2018.04.002); see also Feuvre and Scrutton (2018).

[3]See https://doi.org/10.1038/ncb0710-627.

hESCs is decreasing, while the work of Chinese groups—which have not faced the same constraints—is increasingly being published (Guhr et al., 2018). The growing performance of Chinese groups in hESC research may be an immediate consequence of extensive funding programs and strong political support (Guhr et al., 2018).

Induced pluripotent stem cells (iPSCs) can be derived from adult somatic cells, as described in Chapter 1, and may eventually obviate the need for hESCs for drug discovery, as disease models, and for cellular therapies to cure disease. Because iPSCs are derived from adult cells, however, these lines have acquired genetic mutations and epigenetic modifications over the lifetime of the cell donor that may impact their clinical utility. Thus, hESCs remain the "gold standard" for what may be possible for cellular therapies using iPSCs in the future (Ilic and Ogilvie, 2017), and the majority of current clinical trials are based on hESC-derived cell products (Guhr et al., 2018). In addition to companies conducting trials in the United States, companies in Brazil, China, France, Korea, and the United Kingdom are at the forefront of clinical translation in this arena.

Additional examples of regulatory research constraints include regulations limiting the use and types of animals for research purposes and restrictions related to the use of particular pathogens.

Inadequate Workforce

Growth of the U.S. bioeconomy may be hindered if the quantity or quality of workers with the appropriate skills is insufficient to meet demand. Not only is a skilled workforce necessary to supply U.S. bioeconomy firms with the best possible talent, but a high-quality technical workforce can provide an incentive for foreign bioeconomy firms to establish research and production facilities in the United States.

The ability of the U.S. K–12 education system to engage and prepare students to study science, technology, engineering, and mathematics (STEM) subjects at the university and postgraduate levels has long been of concern. Many studies have offered recommendations for improvement, including improving outreach to minority-serving institutions, devising new mechanisms for undergraduate students to participate in research, and taking part in such programs as the International Genetically Engineered Machine (iGEM) competition (see Box 7-1).[4]

[4]Among the many reports of the National Academies calling attention to the need to strengthen the U.S. STEM workforce are *Rising Above the Gathering Storm* (NAS et al., 2007); *Rising Above the Gathering Storm, Revisited: Rapidly Approaching Category 5* (NAS et al., 2010); *Undergraduate Research Experiences for STEM Students: Successes, Challenges, and Opportunities* (NASEM, 2017d); *Graduate STEM Education for the 21st Century* (NASEM, 2018b); *Indicators for Monitoring Undergraduate STEM Education* (NASEM, 2018c); and *Minority-Serving Institutions: America's Underutilized Resource for Strengthening the STEM Workforce* (NASEM, 2019).

BOX 7-1
Growing the Talent Pool and Advancing a Governance Model for Biotechnology: The International Genetically Engineered Machine (iGEM) Competition

Building a new industry around advances in biotechnology (the bioeconomy) requires increasing numbers of individuals with the necessary skills. Talent development needs to focus beyond technical abilities. The bioeconomy is built upon a wide array of individuals who support, manage, and translate ideas to products. The iGEM competition was established as a pipeline toward this future workforce.[a] At its inception in 2004, the competition involved only teams from the United States. The following year, teams from the United Kingdom and Switzerland joined. In less than 5 years, the United States' share had dropped to slightly more than one-third of teams (34 percent), while one-quarter of them came from Europe (25 percent), slightly more than one-seventh from Canada (14 percent), and about one-fifteenth (7 percent) from China.

Recognizing the international nature of the scientific and engineering enterprise, iGEM includes participants from every inhabited continent. In 2018, more than 6,000 participants in more than 300 teams from more than 40 countries took part. Of those 300 teams, just under one-quarter (23 percent) were from the United States, almost one-third were from China (32 percent), and just under one-quarter were from Europe (23 percent). Teams work on projects of interest and relevance to them across a wide range of areas, including diagnostics, energy, the environment, food and nutrition, foundational advances, information processing, manufacturing, novel applications, therapeutics, and software.

Teams compete for medals (demonstrating technical excellence in synthetic biology) and prizes (for outstanding work in specific areas). They are rewarded for such technical skills as modeling their system, developing genetic parts of maximal future use, and measuring and characterizing their system. They also compete in nontechnical

U.S. colleges and universities can improve the number and quality of their technical graduates, researchers, and educators by continuing to attract high-quality science and engineering students and scholars from overseas. Foreign students constitute a significant fraction of the enrollments at U.S. colleges and universities, particularly in STEM disciplines, and foreign-born employees form a substantial component of the U.S. STEM workforce.[5] Both domestic and international factors may complicate the ability of the United States to continue to attract scientists and engineers to this country.

[5]In the field of biological, agricultural, and environmental sciences, foreign-born scientists and engineers constituted 15.4 percent of the workforce with a bachelor's degree; 27.3 percent of those with a master's degree; and 46.9 percent of those with a Ph.D. in 2015. Note that "foreign-born" is a broader category than individuals who initially arrived in the United States on a (temporary) student or scholar visa; it includes foreign nationals who have immigrated to the United States in any capacity and have attained permanent residency or citizenship (NSB and NSF, 2018).

areas, such as project design, presenting their work, creating posters, documenting their efforts, and entrepreneurship. By applying these technical and nontechnical skills, together with their efforts to create and work in teams; fund, structure, and conduct a project; and "sell" it to both their peers and the synthetic biology community, participants garner key skills that will continue to be important throughout their careers.

iGEM has built a governance framework to ensure that work is safe, secure, and responsible, and intended to instill certain values, actions, and cultural norms rather than regulate the behavior of the community. Since its inception in 2003, iGEM has placed particular focus on how participants' technical work affects the world and how the world affects that technical work—a concept iGEM captures with the term "human practices."[b] Teams are rewarded for integrating such thinking into their technical work and shaping their projects around the needs and views of those affected by or with a stake in their work. They can also be sanctioned for failing to sufficiently address the impact of their work.

The competition also has a robust safety and security oversight framework. This comprehensive and adaptive system ensures that teams are meeting international best practices, as well as complying with relevant national rules and regulations (Millett et al., 2019). Teams are rewarded for excellence in biosafety and biosecurity. They are required to assess risks from their work to themselves, their colleagues, communities, and the environment. They are then expected to plan (and take) measures to mitigate those risks. External experts review these efforts when teams move from the planning to the experimental phase and again when they have finished in the lab and begun to work on how to communicate their findings. A committee comprising diverse experts from around the world works with teams identified as requiring additional support. Teams can be (and have been) sanctioned for failing to meet iGEM's standards.

[a]See https://igem.org.
[b]See https://igem.org/Human_Practices.

Internationally, opportunities for students to remain in their home countries are growing as foreign bioeconomies expand. The world's best science and engineering students and scholars have an increasing number of options for where to study and do research other than coming to the United States. As Federal Bureau of Investigation (FBI) Assistant Director Edward William Priestap testified before a Senate Judiciary Committee subcommittee in June 2018, "Any research institution hoping to be—and to remain—among the best in the world must attract and retain the best people in the world, wherever they are from" (DOJ, 2018b, p. 5). Assistant Director Priestap also called attention to the risk that "some foreign actors, particularly foreign state adversaries, seek to illicitly or illegitimately acquire U.S. academic research and information to advance their scientific, economic, and military development goals." He continued by observing that, "through their exploitative efforts, they reduce U.S. competitiveness and deprive victimized parties of revenue and credit for their

work" (DOJ, 2018b, p. 2). A more detailed discussion of this concern can be found later in this chapter.

Domestically, the United States is increasingly restricting the entry of foreign scholars and students into the country by applying visa controls, which regulate temporary visits and permanent immigration by foreign nationals. The degree of scrutiny applied to visitors depends, among other things, on whether their country of origin poses national security concerns, including the intent to seek illicit access to U.S. technology. Visa controls thus enable the U.S. government to deny access to individuals thought to be supporting such hostile state efforts. However, restrictive visa policies applied to classes of foreign nationals also may have the effect of discouraging the participation of foreign students and scholars in the U.S. bioeconomy research community and workforce more generally, whether as a result of the restrictions themselves or the creation of a perception that the United States is hostile to such engagement. On June 3, 2019, for example, the Chinese government warned students that visas to the United States were increasingly being delayed, denied, and restricted, and the next day warned potential tourists that U.S. law enforcement agencies were "harassing" travelers from China (Zheng, 2019a,b). The same month, Massachusetts Institute of Technology (MIT) President Rafael Reif warned against allowing concerns over academic espionage, well-founded as they might be, to create a "toxic atmosphere of unfounded fear and suspicion" that would send the message that the United States "no longer seek[s] to be a magnet for the world's most driven and creative individuals" (Reif, 2019).

Independent of recent policy changes regarding security screens for foreign students and scholars, U.S. immigration law mandates that applications for student or scholar visas be rejected unless applicants can prove that they have ties to their native country sufficient to compel their return after their U.S. stay. In other words, as stated in a white paper by the Center for Strategic and International Studies, despite the potential contributions that foreign students and scholars can make should they remain in the United States, "the only way they can enter the United States in the first place is by proving their intent to make those contributions somewhere else" (CSIS, 2005, p. 14). It may therefore be difficult to rely on foreign technical expertise to fill gaps in the U.S. bioeconomy workforce.

Ineffective or Inefficient Intellectual Property Environment

Uncertainty over what is considered patentable could have a destabilizing effect on the U.S. bioeconomy by negatively affecting both those pursuing patent protection and those wishing to bring innovations in biotechnology to practice. Since recent Supreme Court decisions have narrowed what is considered patent eligible (discussed below), companies

have experienced more difficulty in obtaining and defending patents on biological innovations. Because patent eligibility is an important consideration for venture capitalists and private equity investors, the greater uncertainty over patent eligibility makes it less likely that firms will invest in biotechnology companies (Taylor, Forthcoming).

Under U.S. patent law, there are two criteria for patent subject-matter eligibility—one statutory, the other judicial. For a claimed invention to qualify as patentable subject matter, it must fall into one of the four statutory categories, defined under 35 U.S.C. § 101 as "any new and useful process, machine, manufacture, or composition of matter." The claimed invention also must not fall into one of the judicial exceptions created through a series of court decisions, namely, abstract ideas, laws of nature, and natural phenomena (including products of nature) (see Manual of Patent Examining Procedure § 2106.04).

In recent years, a number of U.S. Supreme Court decisions have expounded upon the judicial exceptions to patent subject-matter eligibility, including *Mayo Collaborative Services v. Prometheus Labs* (566 U.S. 88; *Mayo*) in 2012, *Association for Molecular Pathology v. Myriad Genetics* (569 U.S. 576; *Myriad*) in 2013, and *Alice Corporation v. CLS Bank International* (573 U.S. 208; *Alice*) in 2014. In *Myriad*, the Court held that

> a naturally occurring DNA segment is a product of nature and not patent eligible merely because it has been isolated, but cDNA [described by the Court as "complementary DNA (cDNA) which contains the same protein-coding information found in a segment of natural DNA but omits portions within the DNA segment that do not code for proteins"] is patent eligible because it is not naturally occurring. (569 U.S. at p. 2)

In *Mayo*, the Court held that "Prometheus' patents set forth laws of nature—namely, relationships between concentrations of certain metabolites in the blood and the likelihood that a dosage of a thiopurine drug will prove ineffective or cause harm," and therefore were not patent-eligible (566 U.S. at p. 8). In *Alice*, the Court affirmed the *Mayo* decision by providing a two-step test of patent eligibility: (1) "determine whether the claims at issue are directed to [a] patent-ineligible concept" (573 U.S. at p. 2) and (2) if the answer is yes, then "search for an inventive concept—i.e., an element or combination of elements that is sufficient to ensure that the patent in practice amounts to significantly more than a patent upon the ineligible concept itself" (573 U.S. at p. 7).

In response to these and other decisions handed down by the U.S. Supreme Court, the U.S. Patent and Trademark Office (USPTO) has continually updated its criteria for evaluating patent subject-matter eligibility (Bahr, 2016, 2018a,b; USPTO, 2014, 2015). In 2017, it issued a formal report on patent-eligible subject matter summarizing the case law, international

approaches to defining patent-eligible subject matter, and the public's view on patent subject-matter eligibility (USPTO, 2017). The most recent guidance on patent subject-matter eligibility was issued in 2019 (USPTO, 2019a,b).

Changes to USPTO examination practice in response to these Supreme Court decisions have had a substantial impact on patenting in biotechnology. Since the *Myriad* decision, patent examiners have been narrowing pending patent claims involving nucleotide sequences not only for applications involving human genomic DNA but also for those covering agricultural products (Jefferson et al., 2015). In response to *Myriad*-based rejections, patent applicants are not "drafting around" the legal principles in *Myriad*; instead, about half (47.6 percent) are abandoning their claims, and about half (47.9 percent) are amending their claims to overcome the rejections (Aboy et al., 2017). Notably, the *Myriad* decision is having a broader impact on biotechnology patent applications beyond those involving isolated genomic DNA. Over a 5-year period after the *Myriad* decision was issued, 6,785 patent applications in Technology Center 1600 (the technology center that provides examination for patent applications in biotechnology and organic chemistry) received a *Myriad*-based rejection, 85 percent of which covered products other than naturally occurring DNA (Aboy et al., 2018).

The *Mayo* decision also has had a substantial impact on patenting in biotechnology. An analysis of patent applications filed in Art Unit 1634 (an art unit responsible for a substantial number of biotechnology inventions) found an increase from 10.5 percent (pre-*Mayo*) to 55.5 percent (post-*Mayo*) in applications that were rejected for not satisfying the patentability conditions in 35 U.S.C. § 101 (Aboy et al., 2019). Even higher rejection rates were observed for patent applications focusing on personalized medicine—an increase from 15.9 percent (pre-*Mayo*) to 86.4 percent (post-*Mayo*) in 35 U.S.C. § 101 rejections (Chao and Mapes, 2016). Among the broader collection of patent applications filed in Technology Center 1600, fully 4,650 (49.3 percent) of applications receiving a *Mayo*-based rejection in the 6 years after *Mayo* was decided were abandoned (Aboy et al., 2019). In addition, *Mayo* has substantially increased the time and costs for prosecuting patent applications in biotechnology. Among the subset of patent applications in Technology Center 1600 that were able to overcome a *Mayo*-based rejection, 45.8 percent had to file one or more Requests for Continued Examination, and 30.3 percent had to file two or more such requests (Aboy et al., 2019).

These decisions also impact granted U.S. patents that are challenged in court. As an example, in *Ariosa Diagnostics v. Sequenom* (788 F.3d 1371 [Fed. Cir. 2015]; *Ariosa*), the Federal Circuit Court affirmed the District Court's finding that the claims of the patent in question are not directed to patent-eligible subject matter and are therefore invalid under 35 U.S.C.

§ 101. The patent at issue in *Ariosa* concerned detecting cell-free fetal DNA in maternal plasma to identify fetal characteristics and abnormalities, an invention that replaces invasive prenatal techniques. Using the two-part § 101 test, the Court found (1) that the claims "are directed to a patent-ineligible concept" because the "method begins and ends with a natural phenomenon" (i.e., cell-free fetal DNA), and (2) the claimed method does not "'transform' the claimed naturally occurring phenomenon into a patent-eligible application" of the phenomenon. The Court did not disagree that "detecting cell-free fetal DNA in maternal plasma or serum that before was discarded as waste material is a positive and valuable contribution to science," but found that "even such valuable contributions can fall short of statutory patentable subject matter."

These findings reveal an unusually high degree of legal uncertainty both in prosecuting patent applications and in upholding the validity of granted patents in biotechnology. And while it is possible to overcome rejections under 35 U.S.C. § 101, doing so requires time and money. Thus, start-up companies with smaller budgets and limited access to patent expertise are more at risk relative to larger, well-established companies.

Although the empirical data collected to date do not provide conclusive evidence that § 101 should be amended, draft legislation to reform § 101 and other sections of the Patent Act has been proposed.[6] The proposed legislation seeks to base patent eligibility on the usefulness of the invention, which is defined to be "any invention or discovery that provides specific and practical utility in any field of technology through human intervention." In essence, the proposed legislation would abrogate the Supreme Court's two-part § 101 test; eliminate judicial exceptions to patent eligibility; and draw strict lines between the inquiries of §§ 101, 102, 103, and 112. A series of public hearings before the U.S. Senate Subcommittee on Intellectual Property featured testimony from a former chief judge of the U.S. Federal Circuit Court, inventors, industry executives, law professors, former directors of USPTO, and such groups as the American Civil Liberties Union. Over the course of these hearings, the lack of consensus on whether the proposed legislation or other reform of U.S. patent law would help or harm innovation in the life sciences and biotechnology became clear. Notably, a letter signed by more than 80 well-established and respected U.S. scientists, including a number of Nobel laureates and recipients of the U.S. National Medal of Science, urged Congress "to perform a thorough study of the nation's requirements for patent eligibility

[6]Senators Tillis, Coons, Collins, Johnson, and Stivers, Draft Bill to Reform Section 101 of the Patent Act, released May 22, 2019, available at https://www.tillis.senate.gov/services/files/E8ED2188-DC15-4876-8F51-A03CF4A63E26.

and of the draft proposal's potential consequences for our country's science and industry, before enacting any relevant legislation."[7]

The constitutional purpose for granting patents is to promote the progress of science and the useful arts (U.S. Const. Art. I, Sec. 8, Cl. 8). Ultimately, the patent system needs to strike a balance in granting exclusive rights that will encourage innovation while not obstructing access to the fundamental tools of science and biotechnology that should be available to all.

Ineffective or Inefficient Regulatory Environment

Excessive or poorly designed regulations could impede innovation by constraining the choices available to innovators or imposing on them requirements that would tend to increase cost or uncertainty. On the other hand, to the extent that regulations are perceived as protecting public health, public safety, and the environment, they can strengthen public trust in a new technology, leading to wider public acceptance and serving as an innovation driver. Where regulations set a high standard of performance that a regulated product must meet, they can also drive the innovation necessary to meet that standard. An example is fuel economy standards for motor vehicles, which have stimulated innovation in improving fuel efficiency.[8]

However, uncertainty in the regulatory environment, more than the regulations themselves, can serve as a drag on innovation. If innovators know what is expected, they can consider regulatory requirements along with other requirements a new product must be designed to satisfy, such as customers' cost and performance targets. But if the regulatory environment is uncertain, an innovator may not know which approach to pursue, and may be reluctant to invest too much R&D funding in areas that might be precluded by later regulatory changes. Uncertainty in the regulatory environment can also discourage innovation by encouraging developers to imitate products that have already charted a path through the regulatory system instead of pursuing innovative products that may have unknown paths with long regulatory delays. The 2016 National Strategy for Modernizing the Regulatory System for Biotechnology Products[9]—intended to reduce regulatory uncertainty by clarifying the roles and responsibilities of current regulatory bodies—and

[7]See https://www.patenteligibility.com.

[8]See https://www.transportation.gov/mission/sustainability/corporate-average-fuel-economy-cafe-standards.

[9]See https://obamawhitehouse.archives.gov/sites/default/files/microsites/ostp/biotech_national_strategy_final.pdf.

the 2019 Executive Order on Modernizing the Regulatory Framework for Agricultural Biotechnology Products[10] represent recent attempts to further streamline the regulatory process. To inform efforts to reduce uncertainty, such studies as the National Academies report *Preparing for Future Products of Biotechnology* (NASEM, 2017a) can give the regulatory system advance warning of innovations that may not fit comfortably within existing regulatory paradigms. It will be important for the regulatory system to continue to track the progress of innovation in the sectors it regulates, and to ensure that it has developed risk assessment procedures and acquired the resources necessary to be able to develop and implement any necessary regulations without unduly constraining the field.

Lack of Public Trust or Conflict with Public Values

A risk to the U.S. bioeconomy of a very different nature derives from societal factors. In recent decades, societal acceptance, expressed either directly by civil society or through the marketplace, has become a potent determinant of which technologies enter practice and which products survive in the market. Full development of the U.S. bioeconomy will be impaired if its products and services fail to win public trust and acceptance or face opposition. Lack of acceptance or opposition can arise from a wide range of concerns, some of which are discussed in this chapter, while others have been articulated in other venues. These concerns include

- the safety, environmental, or land-use implications of the use of genetic engineering in agriculture or of the production of crops for biofuels;
- the consequences of the release or potential release of genetically engineered organisms into the environment;
- lack of confidence in government regulatory bodies;
- the price of biotechnology-derived medical therapies;
- the distribution of economic benefits between producers and consumers, or among producers of different sizes;
- the distribution of economic benefits between those who generate economic value from genetic information and those who had sovereignty over the specimens from which that genetic information was originally obtained;
- the ethics and propriety of modifying human DNA;
- the ethics and propriety of engineering other living organisms;

[10]See https://www.whitehouse.gov/presidential-actions/executive-order-modernizing-regulatory-framework-agricultural-biotechnology-products.

- the application of biotechnology to human reproduction, including the modification of DNA of future generations;
- propagation of misinformation on the Internet that can put public health at risk (see Box 7-2);
- violations of personal privacy due to unauthorized release of one's own genetic information;
- violations of personal privacy due to release of one's relative's genetic information;
- the degree to which risks that might arise from any given biotechnological activity are borne by the beneficiaries of that activity; and
- the potential use of biotechnology by those deliberately seeking to inflict harm.

Some of these concerns can be addressed by science-based assessments to help determine and convey risks of proposed approaches relative to a range of other risks faced by society, including those of not acting. Such assessments can be used to inform regulatory approaches for risk mitigation. However, "a purely technical assessment of risk could result in an analysis that accurately answered the wrong questions and was of little use to decision-makers," to quote one National Academies report summarizing another (NASEM, 2016b; summarizing NRC, 1996). Moreover, quantitative assessments may not even address underlying ethical or social concerns or value conflicts that may be crucial to public acceptance and could potentially be addressed through various engagement

BOX 7-2
Misinformation About Vaccines in the United States

Increasingly, public opinion is shaped by social media and the blogosphere, as well as traditional information sources. Sound science is an important input to public discourse, but it is by no means the sole deciding factor in society's decision making. Unfortunately, on many science subjects, the Internet offers as much misinformation and disinformation as sound information. The bioeconomy presents many examples in which technologies are questioned because of differing opinions as to what is fact.

For example, the long accepted and clearly beneficial use of vaccines to combat infectious disease is now being questioned in the United States (IOM, 2012). Web-propagated misinformation and disinformation have played a significant role in the confusion (Broniatowski et al., 2018). As a result, children's health and public health are at risk. While populations in lower-income countries suffer from lack of *access* to vaccines, some higher-income countries have been more affected by *misinformation* about vaccine safety.

strategies (NASEM, 2016a). There obviously are not right or wrong answers to such questions, but rather a spectrum of viewpoints based on the experiences and values of individuals.

The committee recognizes that public acceptance will be important to the development of the bioeconomy and the realization of its potential benefits. However, public acceptance cannot be addressed at the level of the bioeconomy as a whole. Each product, service, or technological innovation developed by the bioeconomy, like products, services, and innovations arising through other types of activity, will be judged by the public on its own merits, through mechanisms and public engagement approaches that will depend on the particular application involved.

FAILURE TO PROTECT THE BIOECONOMY OR TO PROTECT FROM HARMS MEDIATED BY THE BIOECONOMY

In addition to harms done to the U.S. bioeconomy by the nation's failure to actively promote and support it, the bioeconomy is vulnerable to harm as a result of unfair or illegitimate actions of others, such as the theft of IP, that can harm its competitiveness. Moreover, subversion or misuse of entities within the bioeconomy can cause harm through the accidental or deliberate production and release into the environment of dangerous biological organisms or the corruption of ostensibly beneficial services. As the goods and services offered by the bioeconomy become more widely integrated into the society and the economy at large, adversaries may cause harm through interruption or corruption of bioeconomy operations. Dangerous biological outcomes may be generated through such means as the covert adulteration of biological outputs. And given that the bioeconomy produces goods and services, such as therapeutics and vaccines, that are critical to national security, public health, and public safety, interruption or denial of those goods and services can also lead to societal harm. A healthy bioeconomy must be protected from risks to itself and from the harms that it may pose to the greater society through its subversion or misuse. These risks and harms are discussed in detail in this section.

Constrained Access to International Data

One of the critical inputs for the bioeconomy is data, particularly given the increasing importance of information science, data analysis, and machine learning as a component of the life sciences research process (see Chapter 5). The ability to generate, validate, and use data can be an important source of competitive advantage for biotechnology firms. If foreign datasets are denied to the U.S. bioeconomy as a whole while

foreign entities are able to access U.S. datasets, this lack of reciprocity puts the U.S. bioeconomy at a competitive disadvantage. The same holds true if U.S. firms are forced to release critical bioeconomy datasets to foreign firms as the price of doing business abroad or following a firm's acquisition by foreign entities.

Asymmetric Access to National Sources of Genetic Information

The U.S. government has enabled and supported the creation of rich information databases relevant to the bioeconomy, such as those containing genomic and other "omics" data, remote-sensing data, research publications and their associated raw data, patent data, and census data. To maximize utilization of the results of publicly funded R&D, the U.S. government's "open science" initiatives have sought to ensure the public availability (Van Noorden, 2013)—subject to personal privacy protection—of data maintained by the government or developed through government-funded research. However, this approach is not necessarily emulated by other nations that may have amassed similar databases but are not making them available internationally. In addition, the ability of firms, such as BGI in China, to provide very low-cost DNA sequencing allows them to compete for DNA sequencing contracts from U.S. health care providers or to sequence DNA from clinical samples that are sent to associated Chinese firms for analysis. Should these firms retain (or develop and retain) DNA sequence information from U.S. samples, they would amass a dataset of genetic information from the United States whereas U.S. firms would have no way of accessing a reciprocal dataset given the strict regulations on exporting Chinese genetic data or samples (elaborated on below).

Concerns about asymmetric data access are best articulated in the biomedical arena. An increasing number of efforts are under way in research institutions of all types to sequence the genomes of large portions of the human population in order to gain further insights into disease. Examples include the Cancer Genome Atlas Program of the National Cancer Institute (Cancer Genome Atlas Research Network, 2013); the All of Us Research Program and other national efforts (reviewed by Stark and colleagues [2019]); and the work of private companies such as 23andMe, ColoGuard, and Ancestry.com. The private sector is amassing some of the largest datasets. In 2017, the 23andMe consumer database was used to identify 15 genetic loci associated with depression by obtaining the medical records of 400,000 of the firm's consumers (Hyde et al., 2016). Such achievements exemplify the promise and value of having large, aggregated genomic datasets and the analytic capacity to turn these data into a future product.

However, several countries have enacted policies to prohibit the export of genetic information about their citizens. In 2007, for example, Russia banned the export of all human biological materials, including hair, tissue, and blood, purportedly because the government feared that Western states were developing genetic biological weapons (Vlassov, 2007). Since 2017, Russia has restricted, but not entirely banned, human tissue exports (Bavasi et al., 2017). China does not permit foreign researchers to conduct research involving human genetic resources (genetic materials in human samples or genetic information) unless they are collaborating with a Chinese partner, and the research must be approved in advance by the Human Genetic Resources Administrative Office (Bavasi et al., 2017, p. 2). In 2016, the European Union enacted the General Data Protection Regulation, which expanded health-related data to include genomic and biometric data as "sensitive personal data." This new regulation requires more detailed informed consent to use an individual's data for a secondary purpose unless it has been anonymized. Regarding transnational sharing, the regulation requires that the recipient of the data uphold the same standard of data protection outlined by the regulation (Shabani and Borry, 2018). Brazil has adopted a similar framework that requires additional security measures for sensitive personal data and also has extraterritorial reach (Monteiro, 2018). The United States has not enacted comparable policies at the national level and is therefore directed by a series of guidelines and rules (Majumder, 2018). Given the complexities around data sharing associated with differing regulations, it is unsurprising that transnational data-sharing initiatives are being actively developed to ensure continued access (Fiume et al., 2019).

The impact of these regulations on research is yet to be determined. From a public health perspective, banning the export of genetic information from a country would prevent international scientists from conducting research on genetic diseases that were specific to residents of that country, to the detriment of that country's citizens. From an economic perspective, however, the situation is more complicated. Differences in data protection requirements and ability to share data across the international stage engender concerns about an uneven playing field. If foreign researchers and companies have access to their own countries' biological datasets as well as to corresponding U.S. bioeconomy data, the larger overall amount of data will give them a distinct advantage in identifying genetic disease mechanisms over U.S. researchers and companies, which would have access only to the latter. While the ethnic and racial diversity of the U.S. population may mean that the U.S. data are more valuable—per patient—for the purpose of global pharmaceutical development than data from countries with more homogeneous populations (Gryphon Scientific and Rhodium Group, 2019), this asymmetry still contributes to an

uneven playing field. In addition, asymmetries in access to data may be compounded if other countries have more permissive regulations around how genomic and clinical datasets can be used.

These asymmetries could allow those foreign companies with more extensive datasets to develop therapies before their U.S. counterparts, enabling them to patent and market those therapies first. Again, strictly from a public health perspective, such outcomes—if the therapies could obtain U.S. Food and Drug Administration (FDA) approval—could be seen as advantageous to the United States, whose citizens would benefit from earlier access to therapies than they would have if they had to wait for U.S. firms (with their lesser data sources). Economic and national security problems could arise in the long run, however, if U.S. manufacturers were consistently scooped in their ability to develop their own products, consequently losing profits and market share. If U.S. firms suffered losses to the point where they were unable to stay in business, the U.S. health care system would find itself dependent on foreign pharmaceutical manufacturers for these products, possibly leaving the nation vulnerable to monopoly pricing or even coercion. The U.S. government also possesses databases that are not open to the public in their entirety but can be accessed, often in redacted form, by researchers with appropriate authorization. Such databases include medical records of those individuals for whom the government provides or finances medical care; they also include census information that is available to the public under the condition that information specific to identifiable people or entities be excluded.

The value of these databases to the U.S. and other national bioeconomies, the vulnerability of these databases to access or exploitation, and the effect a country's policy on data openness can have on the relative standing of its own bioeconomy all warrant further scrutiny.

Constraints on Genomic Data as a "Genetic Resource" Under the Nagoya Protocol to the Convention on Biodiversity

The United Nations Convention on Biological Diversity (CBD) has initiated discussions on the relevance of "digital sequence information" to the Convention's goals.[11] This move reflects the changing nature of mechanisms for distributing knowledge or information about a biological entity, which traditionally has relied on the exchange of physical specimens but now may be accomplished by generating and distributing various digital representations of those specimens. The most widely discussed digital representation is an organism's genetic sequence. However, outcome 2 of

[11]See https://www.cbd.int/abs/dsi-gr.shtml.

the Ad Hoc Technical Expert Group on Digital Sequence Information on Genetic Resources[12] illuminated the breadth of what may be considered under this "placeholder" term, which included, among other things, the following (list excerpted from *Annex* to CBD/SBSTTA/22/2):

(a) The nucleic acid sequence reads and the associated data;
(b) Information on the sequence assembly, its annotation and genetic mapping. This information may describe whole genomes, individual genes or fragments thereof, barcodes, organelle genomes or single nucleotide polymorphisms;
(c) Information on gene expression;
(d) Data on macromolecules and cellular metabolites;
(e) Information on ecological relationships, and abiotic factors of the environment;
(f) Function, such as behavioural data;
(g) Structure, including morphological data and phenotype;
(h) Information related to taxonomy;
(i) Modalities of use.

Given that the information enumerated above resides in various public and private data repositories, the question of equitable access and fair distribution of the economic value derived from that information is at the heart of the current discussion on digital sequence information (DSI) with respect to access and benefit sharing. Lai and colleagues (2019) provide a brief overview of the implications of this access to the growing field of synthetic biology. They conclude that policies regarding DSI "could have a significant influence on synthetic biology research and development internationally. For example, implementation of active ABS [access and benefit-sharing] policies on genetic information could inhibit global commercialisation of public-funded research or promote 'get-arounds' to avoid ABS, both of which are not ideal scenarios." Hiemstra and colleagues (2019) provide stakeholder input on the implications of regulating digital sequence information for innovation in multiple biological and ecological domains from the Dutch perspective. They examine the domains of plant and animal breeding, biological research, human health, and use of microorganisms and the field of biotechnology. One of their examples is the widespread use of enzymes in the food industry, arising from diverse sequences derived globally. The authors argue that challenges in trying to track the origin or redistribution of such sequences would be impossible to overcome, and that mandating such efforts would adversely

[12]See https://www.cbd.int/doc/c/704c/70ac/010ad8a5e69380925c38b1a4/sbstta-22-02-en.pdf.

impact biotech start-ups and dampen innovation. They conclude that "ABS arrangements for DSI [digital sequence information] would result in an unforeseeable administrative burden, which consequently leads to large costs, delays in research and slowing down of scientific progress and innovation." Interestingly, they found that Dutch stakeholders felt that "the value of individual genetic resources or DSI is over-rated or overestimated in international discussions. This may result in unrealistic expectations regarding levels of benefit sharing." In accord with this observation is the finding of an independent study that the use of lactic acid bacteria, which underlies the production of all cultured milk products worldwide, would be adversely challenged by certain mechanisms of implementation of the CBD (Flach et al., 2019). Two notable issues raised are that many of the currently practiced or envisioned mechanisms involve bilateral agreements, which become burdensome if not conflicting, and that with existing practices for the global distribution of such products that themselves contain microorganisms, such as yogurt, these agreements bring with them biological samples that are often isolated, genetically improved, and reused in new products.

Use of Bioeconomy Datasets to the Detriment of Individual Privacy or National Security

Two risks associated with bioeconomy datasets involve harm to either individual privacy or national security: exploitation of genetic vulnerabilities and genetic targeting of populations.

Exploitation of Genetic Vulnerabilities

Whole human genomic data, such as those collected by such companies as 23andMe and Ancestry.com, are building the broader informational dataset about genes, inheritance, and subpopulations. A recent study addresses cybersecurity risks specific to human genomic data, data most relevant to biotechnological manufacturing, and human clinical health metadata (DiEuliis, 2018). The emerging landscape in these domains is one of a continuum of potential harms that range from violations of individual privacy, to individual physical harms, to national security concerns (depending on which individuals or populations are at risk).

It has already been demonstrated that individuals can be identified from even portions of their DNA (Dankar et al., 2018; Erlich et al., 2018), and they can be further identified through DNA information gathered on siblings or close relatives (Cohen, 2018; Kaiser, 2018). This finding has implications for individual privacy, safety, and security. Individuals could be targeted for discrimination or manipulation based on genetic

knowledge, and individual biological vulnerabilities could be targeted for physical harm.

Personal knowledge that might be revealed through analysis of these datasets pertains not only to aspects of disease but also to human attributes and behavior, as genomic studies are revealing the underpinnings of complex behaviors and potential ways to manipulate them. Described as "sociogenomics" (Comfort, 2018; Robinson et al., 2005), this arena represents another category of data that could be used to further the intent to do harm. Information about an individual's genotypic predilection for disease or phenotypic behaviors could be used for harm in a social context or to promote discrimination or extortion of an individual. Or there could be known ways to exploit a particular genetic vulnerability to harm to an individual. Electronic health records, health insurance profiles, or other clinical databases in which such data may be housed thus represent important resources that merit protection. In the past few years, comprehensive data thefts have been possible through direct cyberattacks on health information technology infrastructure at large health insurance companies (Ellis, 2018; Ronquillo et al., 2018).

These potential harms become national security concerns when they provide adversaries with a means to elicit personal information about, or even mechanisms to influence, key national decision makers or security personnel, such as members of the military or police forces. It may never be possible to associate a genetic trait with a particular decision; nonetheless, the propensities of national leaders to act in certain ways, which could be influenced by their genetic makeup, could well be of interest to adversarial intelligence agencies. Even if genetic associations with behavior are not well understood at present, they will become better established as more research is conducted and more data are collected and analyzed (Braudt, 2018).

Even if an individual of concern has never provided a genetic sample for the purpose of uploading into a commercial genetic or genealogical database, genomic information is increasingly being derived from medical samples in the pursuit of personalized medicine—the tailoring of medical treatments to a patient's individual characteristics, including genetic makeup. Rapidly decreasing costs for whole-genome sequencing—currently about $1,000 per genome and falling rapidly—are accelerating this trend.[13] And once any such genome is available in a database, it will remain relevant to that person's relatives and descendants forever, albeit decreasingly so as the relationships become more distant.

Similar targeting could be performed using plant or animal genomic data as precision agriculture makes use of individualized genomic

[13]See https://www.genome.gov/about-genomics/fact-sheets/DNA-Sequencing-Costs-Data.

techniques equivalent to precision medicine. Advances in these fields are just as important as those in precision medicine, and are also a target for exploitation.

Genetic Targeting of Populations

Discussions of national security risks posed by access to genetic databases increasingly involve questioning whether "genetic weapons" might be feasible.[14] Such weapons would confer the ability to attack a specific individual or group of individuals on the basis of distinctive genetic traits that those targets would share but that would be very rare or nonexistent in anyone else. Any genetic weapon would require (1) characteristic genetic sequences that can be found in the genomes of the intended target person or population; (2) the corresponding absence of those characteristic sequences in anybody else; and (3) a biological mechanism—say, a DNA construct delivered by a virus—that, when activated within the body, would become highly pathogenic if, and only if, those characteristic genetic sequences were present.

With respect to the first of the above criteria, the science of forensic genetics shows that individuals can be uniquely identified by their DNA. The promise of precision medicine in tailoring medical treatments to individuals or groups on the basis of genetic characteristics and the ability of genetic testing services to categorize people into "haplogroups" that share common ancestors in their patrilineal or matrilineal lines make clear that groups of people who share some common genetic characteristics are increasingly being identified. Whether those groupings correlate with criteria an attacker might seek to target (racial, ethnic, social, political, national, or ideological) is less certain. The two remaining criteria face some additional challenges to overcome. For example, even when genetic signatures have been identified that tend to occur more often in certain groups than in others, they may not form precise distinctions, and they therefore may identify a larger group than was intended. Lastly, the construction of a biological mechanism that could identify a genetic signature and trigger a pathogenic process would entail additional technical challenges.

In summary, developing a genetic weapon that would be able to target selected groups of people preferentially poses a number of technical difficulties. On the other hand, information about the human genome is

[14]Any such weapon based on a biological agent would violate the Biological and Toxin Weapons Convention. Discussion of "genetic weapons" is not meant to imply that they would be legally acceptable or even technically feasible yet.

growing rapidly, and new biotechnologies are continually being developed that lower the barriers to mastering various biological processes. As with the other biosecurity concerns discussed later in this chapter, this area of research will require continual monitoring.

Potential for Violation of Personal Privacy, Utilization by Law Enforcement, and Genetic Discrimination

The popularity and availability of direct-to-consumer (DTC) genetesting kits have soared in recent years, with hundreds of such DTC services becoming available and an estimated 15 million people taking part as of April 2018 (Erlich et al., 2018; Martin, 2018). Although genetic testing provides a wealth of information, concerns remain about the privacy of genetic information. While some of the more popular services, such as 23andMe, are very explicit about their privacy policies (Martin, 2018), most such services are not. A study of the privacy policies of 30 different DTC genetic testing companies found that most "do not consistently meet international transparency guidelines related to confidentiality, privacy, and secondary use of data" (Laestadius et al., 2017).

Additionally, there are risks associated with linking genetic data to personal information that is posted to such databases as GEDmatch. While these public third-party services have classically been used to identify distant relatives by matching genetic information procured from DTC companies, this use does not exclude the ability to use this information for other purposes. And one study showed that 60 percent of individuals with European ancestry in the United States can be linked to at least one individual in the GEDmatch database who is considered a close relative. Recently, law enforcement has been utilizing third-party genetic information websites to identify criminals, predominantly in cold cases (Saey, 2018). Using genetic evidence gathered at crime scenes, law enforcement can find relatives with close genetic ties to criminals and subsequently develop a list of suspects. These suspects can then be confirmed by direct genetic testing (Saey, 2018). The most famous of these cases is the recent identification of the Golden State Killer, who was active between 1974 and 1986 but was identified and arrested in 2018 following the use of genetic genealogy (Jouvenal, 2018). In response to this lack of privacy with respect to law enforcement, GEDmatch adopted a new privacy policy in May 2019 requiring its users to opt in to use of their genetic information by law enforcement (Aldhous, 2019).

The U.S. Department of Defense maintains a repository of DNA reference specimens for all active duty and reserve service members, but a court order is required to release them, and only for the purpose of

"investigation or prosecution of a felony, or any sexual offense, for which no other source of DNA information is reasonably available."[15]

In September 2019, the U.S. Department of Justice adopted an interim policy that establishes requirements for the use of this type of genetic analysis by law enforcement. One requirement is that investigative agencies identify themselves as law enforcement to the genetic genealogy services they use, and that they utilize only genetic genealogy databases that have explicitly notified their users that law enforcement may use their services to investigate crimes or identify human remains. The interim policy also sets out how the practice is to be used to generate leads for unsolved crimes (DOJ, 2019; DOJ Office of Public Affairs, 2019).

Another consequence related to the rise of genomic sequencing is the potential for genetic discrimination. As discussed in the earlier section on genetic targeting of populations, genetic discrimination can be based on genetic characteristics within a group of genomes, as well as individual genetic characteristics. The most prominent example of group discrimination and surveillance is the use of genetic sequencing by China to identify Uighurs, a Muslim ethnic group. Members of this ethnic group were identified by the Chinese government under the guise of health-related genetic testing, but with the purpose of placing them in "re-education camps" to be "more subservient to the communist party" (Wee, 2019).

Genetic testing also allows for discrimination against individuals based on their genetic predisposition to traits or diseases. Congress took action to mitigate this problem in 2008 by passing the Genetic Information Nondiscrimination Act (GINA), which prohibits discrimination by employers and health insurers based on genetic information, but it fails to cover many other critical areas in which discrimination is possible, such as life insurance or health care plans from employers with fewer than 15 employees. Some states passed their own policies to close these gaps. California, for example, enacted its comprehensive CalGINA, covering discrimination in many scenarios, including life insurance and disability insurance.[16]

One example of individual genetic discrimination is a child, Colman Chadman, of Palo Alto, California, who had genetic markers for cystic fibrosis (CF) without having the disease. Chadman was attending a school where there were two other children with CF, but was dismissed because of the possibility that multiple children with CF in the same school could enable the possibility of transmitting infections (the other two children were siblings and therefore allowed to stay together in school). His family

[15]10 U.S.C. § 1565a, "DNA samples maintained for identification of human remains: use for law enforcement purposes."

[16]See https://www.genome.gov/about-genomics/policy-issues/Genetic-Discrimination.

subsequently sued for genetic discrimination on the grounds that Chadman had only genetic markers for CF, but not the disease (Zhang, 2016). As genetic information becomes more reliable and reveals more information about individuals, it can open opportunities for new avenues of genetic discrimination.

Another risk is the social instability that could occur if GINA were repealed or weakened. As the economic value and predictive power of information in the human genome increase, certain industries will be able to make increasingly powerful economic arguments for having access to and being able to use human genome information in their decision making.

Cyber Risks Associated with the Bioeconomy

With the increasing reliance on large aggregated datasets, the emerging bioeconomy now exists at the intersection of information science and biotechnological science. The digitization of biology—most literally, the conversion of nucleotide codes of DNA to machine-readable formats—is transforming all the life sciences. DNA sequences can now be databased, mined, and used for in silico experimentation or design. To fully extrapolate digital information into meaningful biological systems or the creation of engineered organisms requires more than representation in machine-readable formats. The leap from the nucleotide data sequences recorded in databases to tangible biological predictive form and function is referred to as "abstraction" (Ochs et al., 2016), and will be enabled only through deeper understanding of how genomic sequence underpins function and phenotype, using a complex set of computational tools, algorithms, and bioinformatics programs. Abstraction would enable a future biological engineer to sit at a computer interface and simply type in desired phenotypic features for a biological protein/enzyme, or even an entire microbe or plant cell, and receive those designs as outputs without directly knowing the genetic sequences responsible for those phenotypes. The more complex the organism is, the greater the computing and data storage power that will be required.

A second important advance is automation, which increasingly drives biological manufacturing platforms—machines can now do much of the work that previously could be accomplished only by human physical handling. Furthermore, automated devices that monitor and/or control biological and physiological processes produce reams of data in highly parallelized sets of experiments, running 24 hours per day, which can be shared and stored through cloud computing networks, and as noted above, the operation of such devices requires advanced computational software, algorithms, and bioinformatics. Moreover, increasing amounts

of data are generated during the monitoring and control of bioeconomy-related commercial manufacturing processes, and it is critical to these commercial enterprises that such data be secured and protected as part of a quality management system (Mantle et al., 2019).

Resources in the bioeconomy are valuable, both commercially and because of the risk to life, national security, health, and property if a malicious party should tamper with, access, or otherwise manipulate the data. For the past 20 years, most malicious hacking has been goal-directed, with financial or national interests as the primary motivators. As Table 7-1 demonstrates, bioeconomy companies are major targets for both of these motivators. Many of the most sophisticated cybersecurity attacks will likely originate from or be abetted by foreign intelligence agencies. Such agencies can bring to bear more technical skills and more resources than can ordinary criminal hackers. These skills and resources include what one former National Security Agency official has called "the three Bs: burglary, bribery, and blackmail" (Smith and Marchesini, 2007). Note that these attacks may specifically target corrupt or coerced employees, that is, people who have authorized access to computer systems and who are inside many firewalls.

The bioeconomy's growing reliance on software, networking, and computer hardware tools yields the same cyber vulnerabilities present in any other sector, which can be viewed as fundamental cybersecurity risks. Cybersecurity here, as in other sectors and domains, is typically concerned with hacking, sabotage, or other compromise of cyber controls that can result in disruption, breached privacy, or theft of IP. These kinds of activities can have adverse impacts on the bioeconomy, and furthermore, on the U.S. economy writ large. A recent report from the White House estimates that malicious cyber activity imposes costs on the U.S. economy (through the theft of IP and personally identifiable information, denial-of-service attacks, data and equipment destruction, and ransomware attacks) that ran as high as $109 billion in 2016 (Council of Economic Advisors, 2018).

Understanding of the security vulnerabilities that may derive from cyber intrusions has recently generated discussion of what is referred to as "cyberbiosecurity" (Murch et al., 2018; Peccoud et al., 2018). Cyberbiosecurity has been described as bringing together "disparate communities to identify and address a complex ecosystem of security vulnerabilities at the interface of the life sciences, information systems, biosecurity, and cybersecurity" (Richardson et al., 2019). Bioinformatics datasets, other input tools or data, or industrial process control systems used by a biotech facility could be vulnerable to tampering, which could result in damage to the facility or the subversion or sabotage of its products, and subsequent harm to people, plants, animals, or the environment

TABLE 7-1 Cybersecurity and the Bioeconomy: A Timeline of Selected News and Events

Date	Event
July 9, 2019	Research Team Identifies Vulnerabilities in GE Medical Devices
July 1, 2019	Sandia National Laboratories Identifies Vulnerabilities in Genomic Analysis Software
June 27, 2019	U.S. Food and Drug Administration Warns of Cybersecurity Risks in Insulin Pumps
June 26, 2019	Reuters Reports Cloud-Based Attacks Against Syngenta
June 21, 2019	Dominion National Reports Data Breach
June 14, 2019	ZDNet Reports Iranian Hackers Targeting DNA Sequencer Applications
May 10, 2019	American Medical Collection Agency Data Breach
April 30, 2019	Charles River Lab Notifies Clients of Data Breach
April 26, 2019	Inmediata Health Group Notifies Patients of Data Breach
April 25, 2019	Doctors Management Services Discloses Ransomware Attack
April 4, 2019	Bayer Reports Intrusion into Computer Systems
March 22, 2019	Navicent Health Announces Data Breach
March 21, 2019	Oregon Department of Human Services Announces Data Breach
March 7, 2019	Columbia Surgical Specialists of Spokane Announces Ransomware Attack
February 22, 2019	UConn Health Notifies Patients of Data Breach
February 22, 2019	University of California Researchers Reveal "Acoustic Side-Channel Attack"
February 20, 2019	University of Washington Medicine Announces Online Exposure of Patient Information
December 5, 2018	Iranian Nationals Charged in Relation to SamSam Ransomware Attacks on Atlanta
November 28, 2018	U.S. Department of Justice Unseals Indictment Against Iranians in Relation to SamSam Ransomware Attacks
November 27, 2018	Atrium Discloses Unauthorized Database Access
November 16, 2018	Episcopal Health Services Notifies Individuals of Data Breach
October 25, 2018	Bankers Life Announces Data Breach
September 11, 2018	Health Management Concepts Discloses Ransomware Attack

continued

TABLE 7-1 Continued

Date	Event
August 16, 2018	Augusta University Notifies Patients of Spear-Phishing Incident
July 30, 2018	UnityPoint Health Notifies Patients of Data Breach
July 19, 2018	Laboratory Corp. of America Suffers SamSam Ransomware Attack
July 10, 2018	MedEvolve Discloses Data Breach
June 14, 2018	Med Associates Discloses Data Breach
April 17, 2018	Sangamo Therapeutics Files SEC Report Detailing Compromised Emails
March 22, 2018	Atlanta Officials Announce SamSam Ransomware Attack
January 18, 2018	Allscripts Reports SamSam Ransomware Attack
January 5, 2018	Oklahoma State University Center for Health Sciences Discloses Data Breach
August 10, 2017	Researchers Reveal Technique for Encoding Malicious Software into Synthetic DNA
June 27, 2017	Merck and Co. Suffers NotPetya Ransomware Attack
May 12, 2017	Britain's National Health Service Attacked by WannaCry Ransomware
January 15, 2017	Indiana Cancer Nonprofit Announces Cyber Attack
October 13, 2016	Peachtree Orthopedics Suffers Data Breach
August 25, 2016	MedSec Cybersecurity Researchers Report Vulnerabilities in Pacemakers
March 29, 2016	Security Researchers Identify Vulnerabilities in Medical Dispensing Systems
March 23, 2016	Verizon Details Cyber Attack Against Water Treatment Plant
February 11, 2016	Hollywood Presbyterian Medical Center Hit with Ransomware Attack
July 17, 2015	UCLA Health System Discloses Data Breach
February 5, 2015	Anthem Discloses Breach of Customer Data

NOTES: Dates reflect when the incidents were first reported. GE = General Electric; SEC = Securities and Exchange Commission; UCLA = University of California, Los Angeles.
SOURCES: This information was provided to the committee as an early draft of a study undertaken by the Carnegie Endowment for International Peace, conducted by Katherine Charlet (a committee member), Natalie Thompson, and Frances Reuland. See https://carnegieendowment.org/programs/technology/biotechnology/timeline (accessed December 1, 2019).

(Peccoud et al., 2018). Similarly, corruption of environmentally or health-related sensors or data could result in the misapplication of health care or environmental remediation. For example, preventing sabotage of biological containment systems that could cause the environmental or occupational release of certain dangerous pathogens is a required component of security plans for those types of facilities (CDC and USDA, 2017a), but these considerations may not have been evaluated for other components of the bioeconomy that pose similar risks. Given that the security plans of containment labs consider cyber intrusions along with insider threats (CDC and USDA, 2017b), they may offer a useful model for information systems security controls for other bioeconomy components.

The growth of cloud computing and cloud storage will pose new challenges. On the one hand, cloud systems are often inherently more secure because they are administered by specialists. On the other hand, users of these cloud systems need to configure their portion—particularly access controls—properly if security is to be maintained. It is not possible to predict which aspect will dominate, especially if organizations attempt to share some portions of their cloud storage.

Although there is no one model for the use of information systems across the bioeconomy, a few important common features can be identified:

- The bioeconomy relies on large databases, often of commercially or personally sensitive information.
- Some components of the bioeconomy rely on open-source software packages, often of uncertain quality, robustness, and degree of maintenance.
- The bioeconomy relies on Internet communications to exchange data (such as publicly available genome data). Proprietary systems are often used to ensure safety and compliance with applicable regulations for commercial products and processes.

None of these features is unique to the bioeconomy, but their particular manifestation in the bioeconomy is notable. For example, while many commercial datasets involve such personal information as addresses and credit card numbers, the datasets in the bioeconomy (and data being exchanged over the Internet) may include full genetic sequences of humans and other organisms. Arguably, the features described above are thus materially different when understood in the context of the bioeconomy—because the genetic information literally defines us as humans and enables manipulation at the level of life's component parts. The bioeconomy enables an overlap of privacy risk and the risk of physical harm. As noted earlier, understanding the genetic makeup of an individual can

reveal such vulnerabilities as the propensity for certain diseases and that information could in turn be used to harm a person or group of people.

Within today's bioeconomy, large corporations are aware of traditional cyber concerns and utilize information technology infrastructure to protect against common threats. However, they may be less aware of the possibility of specific unwanted biological outcomes and their sequelae. Smaller companies or biotech start-ups may not view themselves as cyber targets, or if they do, they may not have the resources to address the risks adequately. Small companies and start-ups are generally more vulnerable to cyber intrusions relative to large organizations. Even if they have skilled information technology departments, such organizations typically have neither the budget nor the security focus to fend off attackers, nor do they have much actual experience in this arena (Hiscox, 2018). They may not employ state-of-the art defenses, such as multifactor authentication, and users who have not been properly educated on these matters are more likely to fall for phishing attacks and the like. In addition, most application programmers have little, if any, education in how to write secure code, opening the door to even low-end attackers.

Addressing cyber concerns also will depend on the commercial availability of mitigation measures. If tools tailored specifically to the biotechnology realm are required, awareness is needed among cybersecurity professionals, who at present have little interaction with bio-specific concerns. Thus, not all of the responsibility for addressing cyber concerns lies in the biotechnology industry and life sciences research space; many cyber-focused programs lack awareness of the particular challenges that research in the life sciences or biotechnology industries may face.

Risks Related to Cyber-Physical Systems

In the bioeconomy, some more novel dimensions of risk beyond fundamental cybersecurity must be considered. These include in particular cyber intrusions that result (whether intentionally or unintentionally) in unwanted or dangerous biological outcomes. Some of these security vulnerabilities have been described previously (Peccoud et al., 2018). One way in which some bioeconomy software, together with associated systems, differs from run-of-the-mill enterprise software is that some of it controls physical devices, such as DNA synthesizers or building services equipment in biological containment labs. Cyber-physical systems pose significant security and safety risks since their compromise can have effects on the real world; in this case, those effects could include faulty or even dangerous synthesis of biomaterials or interference with biological containment systems.

The challenge of securing cyber-physical systems is especially grave because the control computers involved are sometimes running obsolete, unsupported operating systems. Briefly, the lifetimes of the controlled devices (hardware) are often much greater than those of the operating systems (software) on which they rely. As long as the physical functioning of the devices is adequate to the task at hand and they meet any certification requirements, they are typically kept in service. This can be true for many of the devices used in the bioeconomy for research purposes because they are often quite expensive or difficult to change; therefore, discarding them when the operating system or software running on them is obsolete is often not an option. In commercial settings, updating of software or devices because of security concerns is frequently hampered by regulation rather than cost (Williams and Woodward, 2015). In a recent survey of international leaders in biotechnology and cybersecurity, more than 90 percent of respondents expressed the belief that insufficient time and resources were being dedicated to cyber risks to biological equipment and facilities (Millett et al., 2019). If, however, there was a shift in industry practice and the requirements for certification were to emphasize security and appropriate security updates for the lifetime of the device, progress could be made. It is likely impossible, or at best difficult, to retrofit this sort of certification requirement to existing devices, but with lead time, sensible requirements, and well-considered guidance, device manufacturers would be able to comply with new security requirements. There would be costs, but if embedded device manufacturers had to plan for security as a long-term attribute of their products, they would engineer them in such a way as to provide cost-effective lifetime security.

Risks Related to Datasets

Another way in which bioeconomy software is distinct is that some of it operates on very large, very sensitive datasets. Some of these datasets may contain individuals' genomic or medical data, in which case they entail serious personal privacy risks; others may contain proprietary DNA sequences or other data used to make products that will compete in the marketplace. A variety of operations are performed on these databases, increasingly including use of machine learning and other artificial intelligence techniques that can, for example, associate a protein's amino acid sequence with its three-dimensional structure or identify pathways for and optimize the production of biosynthesized materials, or—particularly in association with other sources of data such as medical records—"identify the relations between genetic characteristics and the response to specific treatments" or identify new drugs "by training a classifier on a dataset where functioning and nonfunctioning drugs have been

identified" (Oliveira, 2019). Use of these data is vital for the bioeconomy, but they require a great deal of protection. The risk component in this arena is the theft of genomic, medical, or other biotechnological data that could be used to advance a competitor's efforts or even an adversary's bioeconomy. In such cases, direct harm to privacy or to an individual may not be the outcome; rather, harm may result from subsequent inappropriate use of the data. Such harms could include the ability to outcompete the United States by inappropriately amassing larger, more comprehensive biotechnology datasets, thus putting the United States at potential economic disadvantage or forcing it to acquire needed products outside its own bioeconomy (as described previously in the chapter).

The integrity of datasets is also a serious issue. To protect them, they could be digitally signed, although there might be difficult questions about the proper public key infrastructure for this purpose. A digital signature, at best, attests that some party believes that certain content is authentic; it does not, however, state that the *proper* party believes that. Digitally signed datasets are self-authenticating; as such, they can be safely redistributed by other parties or via peer-to-peer mechanisms, such as BitTorrent.

Vulnerabilities Due to Reliance on Open-Source Software

A large portion of the bioeconomy runs on open-source software, often derived from university research projects. Indeed, the U.S. Department of Energy's (DOE's) Systems Biology Knowledgebase (KBase)[17] provides a centralized repository of open-source software numbering in the hundreds for web-registered users, to which developers can contribute new tools (Arkin et al., 2018). Sharing of "narratives" by researchers speeds the analysis of data by new users, and new tools are generated using a software development kit that helps ensure compatibility in workflows. Researchers conduct their in silico experiments and analyses within this free and valuable community resource after registering for an account (Arkin et al., 2018). Because the site is extensively curated, KBase itself may be insulated from some vulnerabilities associated with open-source software. While there is no a priori problem with open-source software—indeed, it is a valuable resource for the community—the software industry has learned that simply making code open-source does little or nothing to guarantee its quality, robustness, and security.

Failure to update open-source components included in some large product or system often means that security holes will persist long after the hole has been patched in the upstream packages. Given how popular

[17]See https://kbase.us/what-is-kbase.

some open-source packages are, many systems that use them can experience common failures (NASEM, 2017c). Furthermore, the security of a codebase is intimately tied to its overall quality: a high percentage of system penetrations are due to buggy code.

Supply chain attacks in the software ecosystem are another risk to the bioeconomy. The provenance of open-source software is often unclear, without an audit trail showing who made which changes, when, and why. Furthermore, there may be no systematic approach for tracking or repairing bugs.[18] These procedural lacunae leave open the potential for vulnerabilities to be deliberately introduced into the software: a malicious party could plant malware in a bioeconomy software package under the assumption that it will someday be used by a bioeconomy company. Although proprietary software would not share the risk that anyone would be free to engineer flaws into the software, it can also pose supply chain risks, not least due to the risk of compromised insiders (Black et al., 2016).

Cybersecurity Protections and Defense in the Bioeconomy

The discussion above describes a number of digitization- and cybersecurity-related risks to the bioeconomy. Fortunately, most of the attacks that can be expected are not as sophisticated as those launched or abetted by intelligence agencies, and can be dealt with via standard, off-the-shelf defensive cybersecurity tools—tools routinely used by many companies. For example, one best security practice is to ensure that all network connections are encrypted. This measure is not so much for confidentiality as for the connection authentication that is part of standard encrypted connections. Similarly, since phishing for user credentials is a ubiquitous attack vector, another best practice is to ensure that all logins (especially for email) are protected via multifactor authentication. That said, more sophisticated attackers do exist, and must be planned for; however, even nation-states tend to try simpler attacks first.

Information sharing Stakeholders in the bioeconomy sector may find it useful to develop and sustain cooperative structures that enable sharing of cyberthreat information. Many infrastructure sectors have developed capabilities to share information on cyberthreats among sector members. Such information sharing is valuable because it helps identify potential cyberthreats and share best practices for protecting against them.

[18]We note that this is not an inherent problem for open-source software. A number of packages, such as the Apache web server and the Firefox web browser, do use state-of-the-art software engineering practices.

Cyberthreat actors, including foreign intelligence agencies, sometimes pursue broad campaigns not just against one company but against entire sectors. Robust information sharing thus helps spread information that enables companies to take quicker mitigating action to counter these campaigns.

In certain critical infrastructure sectors, Information Sharing and Analysis Centers (ISACs) are key entities in facilitating information sharing.[19] These organizations provide a central place for companies to distribute cyberthreat indicators, receive warnings from government agencies, facilitate training, and act as a cybersecurity resource for the sector.

More recently, the U.S. Department of Homeland Security has encouraged the development of Information Sharing and Analysis Organizations (ISAOs). ISAOs are similar to ISACs in that they provide a forum for sharing information on cyberthreats, but because they do not align with specific critical infrastructure sectors, they can be more flexible in their approach and membership. For example, companies can form a regional ISAO even if they come from diverse sectors.

Companies across the bioeconomy would benefit from participating in a cyberthreat information-sharing organization. However, there is no broadly applicable "fit" for bioeconomy companies within the current structure. Because ISACs are tied to specific critical infrastructure sectors, no single ISAC obviously aligns with the bioeconomy, although some, such as the National Health and Research & Education Network ISACs, would overlap with some portion of bioeconomy stakeholders.[20] ISACs vet new members to ensure that they will protect sensitive information that is shared by other members, which means ISAC participation may be more difficult for some members of the bioeconomy, such as start-ups or other companies without much corporate history, than for others.

There are also unique information-sharing needs for the bioeconomy that may not be filled by existing structures. For example, if only the health-focused members of the bioeconomy were sharing threat information with one another, it might be difficult to identify and understand a

[19]Critical infrastructures are those assets, systems, and networks that are considered so essential "that their incapacitation or destruction would have a debilitating effect on security, national economic security, national public health or safety, or any combination thereof" (see the U.S. Department of Homeland Security website at https://www.dhs.gov/cisa/critical-infrastructure-sectors).

[20]Presidential Policy Directive 21, "Critical Infrastructure Security and Resilience" (White House Office of the Press Secretary, 2013), identifies 16 critical sectors: chemicals; commercial facilities; communications; critical manufacturing; dams; defense industrial base; emergency services; energy; financial services; food and agriculture; government facilities; health care and public health; information technology; nuclear reactors, materials, and waste; transportation systems; and water and wastewater systems.

(hypothetical) adversary cross-sector campaign, involving entities outside health care, to steal bioeconomy-related IP or data. Although it would be possible for bioeconomy stakeholders to form an ISAO, start-up costs are entailed in building such a structure.

Improved software engineering With respect to software development and software quality generally, more attention to standard software engineering techniques—unit tests, regression test suites, code reviews, and the like—will pay off in more reliable and more secure code. Computational biologists who come to the field from biology, as opposed to computer science, often lack the relevant training. In addition, there are security-specific practices that should be adopted, including use of specialized tools that look for likely insecure constructs.

It is not feasible to demand that every graduate student research project conform to such standards. Indeed, such standards are uncommon even in computer science departments, let alone biology departments. That said, it would be useful if core open-source bioeconomy software—major programs used by a significant number of companies—were brought into a more formal regime, such as a repository. That is, some version would be captured, audited, and placed under formal change control, with a formal testing regimen and changes restricted to authorized personnel. This process need not and should not change the open-source nature of the software, and anyone would remain free to download it and modify it as desired; changes, though, even those contributed to the package by some user or company, would need to go through an auditing and testing process.

Such a repository could be run by an ISAC-like entity or other special-purpose consortium. Note that it is unlikely that access to the "official" source code within the repository could be restricted to ISAC or consortium members; many open-source packages use the GNU Public License, which bars restrictions on redistribution.

Improved dataset sharing With respect to the challenge of securing large, safety- and/or privacy-critical datasets, one possible approach is to use a variety of advanced cryptographic techniques. There is a subfield of cryptography known as secure multiparty computation, or simply multiparty computation (MPC), in which operations are performed on encrypted data. The party performing the computations cannot read the data, but the ultimate answer, when decrypted, will be correct. It has been shown mathematically that any computation can be done that way, although the proof is not useful for implementations; the resulting programs are many orders of magnitude slower than a simple calculation using unencrypted data. Instead, special-purpose solutions are sought for each class

of problem. This approach, though in some theoretical sense unsatisfying, has proved quite successful. Encrypted search—picking out the right records from an encrypted database—often takes only a small integer multiple of the time required for a native database query.[21] Given how fast today's computers are, this slowdown is quite acceptable.

Other research has been done on privacy-preserving machine learning, which allows identifying information to be removed from databases while leaving them useful for research (Al-Rubaie and Chang, 2018). This technology may also resolve tensions with some countries about export of their citizens' data, at least where the objections are rooted in privacy principles and not protectionism. Privacy-preserving machine learning does, however, have limitations, not so much in the algorithms themselves as in the database anonymization process: the effort to protect privacy can obscure crucial details necessary for adequate results (Fredrikson et al., 2014). Further research will be required in this area before wide-scale application can be expected. Furthermore, there are many desired operations for which no MPC algorithms exist.

Economic Attack: Theft and Infiltration

Theft or Misappropriation of Trade Secrets

Theft of trade secrets poses a substantial risk to biotechnology companies. Because of the risks posed by disclosing information in patents (see Box 7-3), many biotechnology companies decide to protect their IP assets as trade secrets instead. As illustrated by *Genentech, Inc. v. JHL Biotech, Inc*. (No. 3:18-cv-06582-WHA [N.D. Cal. 2019]), trade secrets may be stolen by trusted employees to advance the interests of other parties, including companies outside the United States. In that case, four former employees of the U.S.-based biotech firm Genentech, Inc. were indicted for stealing trade secrets to assist JHL Biotech, Inc., a Taiwan-based company, in developing and manufacturing biosimilar versions of Genentech medicines. The complaint alleges that hundreds of files containing confidential information were downloaded from Genentech's secure document repository system, including the company's proprietary, FDA-approved analytical methods; formulation know-how; quality acceptance criteria; and manufacturing protocols and procedures for establishing and maintaining safe, sterile manufacturing facilities and equipment.

In addition to theft of confidential documents, proprietary seeds or strains may be stolen and passed on to other companies. In 2018, for

[21]For a summary of encrypted search techniques, see http://esl.cs.brown.edu/blog/how-to-search-on-encrypted-data-introduction-part-1.

example, a Chinese scientist who worked as a rice breeder for Ventria Bioscience in Junction City, Kansas, stole genetically engineered rice seeds that expressed recombinant human proteins (DOJ, 2018a).

Illicit Transfer of Knowledge and Technology via Academic Misconduct

The U.S. government has recently become concerned about inappropriate actions taken by foreign students and scholars in U.S. research institutions. In congressional testimony, FBI Assistant Director Priestap stated that U.S. academic environments offer "valuable, vulnerable, and viable targets for foreign espionage" that are exploited by some foreign visitors, who steal "unpublished data, laboratory designs, grant proposals, experiment processes, research samples, blueprints, and state-of-the-art software and hardware" (DOJ, 2018b, p. 3). He also warned that visitors can exploit the open environments of these institutions, enabling them to spot talent and collect insights.[22] Of particular concern, he said, is the use of foreign academics by their home countries' intelligence services, which do not necessarily send or task academics with particular objectives, but rather seek to leverage them once they return home for a visit or upon the completion of their studies.

Of particular concern to some U.S. government officials are foreign talent recruitment programs, such as China's Thousand Talents Program, through which foreign countries offer salaries, research facilities, and titles to induce expatriate scientists and other overseas experts to bring their knowledge and experience to China. China describes its Thousand Talents Program as a search for "strategic scientists or leading talents who can make breakthroughs in key technologies or can enhance China's high-tech industries and emerging disciplines."[23] The program seeks to recruit Chinese scholars currently living and working aboard, entrepreneurs, non-Chinese scholars, and younger scholars for long- and short-term appointments. U.S. officials characterize such programs as "compounding the threat" and encouraging the theft of IP (DOJ, 2018b, p. 4), and official presentations have described access to IP as these programs' "key qualification" (NIH, 2018, chart 7).

Coincident with issuance of these warnings, NIH sent letters to more than 10,000 research institutions warning that "some foreign entities have mounted systematic programs … to take advantage of the long tradition

[22]In addition to conducting illicit technology transfer, Priestap stated that foreign visitors exploiting access to U.S. institutions can introduce propaganda platforms, conduct training, recruit on behalf of foreign intelligence agencies, and stymie freedom of speech.

[23]"The Thousand Talents Plan," 1000plan.org.cn/en/history.html.

BOX 7-3
Choosing Between Patent Protections and Trade Secrecy

In developing an intellectual property (IP) strategy, biotech companies must decide whether patents or trade secrets are best suited for protecting their innovations. Because the public disclosure requirements are vastly different, and because patents and trade secrets are mutually exclusive for a given innovation, the choice between patent protection and trade secrecy must be carefully considered. The quid pro quo of the patent system is that companies must disclose information about an invention to obtain a patent. Patents provide companies with a limited period of exclusivity (generally 20 years from the date of filing) for an invention in exchange for disclosing information about the invention to the public. It is important to keep in mind that patents provide a *negative* right: they do not give companies permission to practice their invention, but the ability to prevent other companies from practicing it, even if one of those other companies legitimately came up with the invention on its own. By comparison, trade secrets can be held indefinitely as long as appropriate precautions are taken to avoid disclosure. Trade secrets do not guarantee exclusivity, however, because other companies that legitimately come up with the same or a similar invention on their own are free to practice their invention.

While patent systems generally require disclosure of an invention, the United States is unique in also requiring applicants to disclose their "best mode" of practicing the claimed invention. Specifically, 35 U.S.C. § 112(a) states: "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor or joint inventor of carrying out the invention."

The case of *Ajinomoto Co., Inc. v. International Trade Commission* (No. 18-1590 [Fed. Cir. 2019]; *Ajinomoto*) provides an example of the disclosure required when seeking patent protection for products made using engineered strains. In *Ajinomoto*, the asserted claims of U.S. Patent Nos. 5,827,698 and 6,040,160 were deemed invalid for failure to comply with the best mode requirement. Both patents were directed at improved methods of producing L-lysine using genetically modified *E. coli* bacteria. Although the patents did disclose certain *E. coli* strains used for practicing the claimed inventions, the patents were deemed invalid because the inventors had violated the best mode requirement by failing to disclose their preferred host strain, which contained additional

of trust, fairness, and excellence of NIH-supported research activities."[24] The letter highlighted three areas of concern, which it said were not limited to biomedical research but have long been posed as well by defense and energy research: diversion of IP; sharing of confidential information from grant proposals; and failure to disclose resources obtained

[24]Letter from NIH director Francis Collins, August 20, 2018, available at https://www.sciencemag.org/sites/default/files/NIH%20Foreign%20Influence%20Letter%20to%20Grantees%2008-20-18.pdf.

nonclaimed genetic mutations for producing lysine in culture. The Federal Circuit Court held that "the inventors could not, consistent with the best mode requirement, claim the cultivation of a bacterium containing a mutation in the lysine decarboxylase gene while simultaneously keeping from the public the identity of the one and only bacterium they used to practice that cultivation."

As *Ajinomoto* illustrates, it is not possible to obtain a patent on an invention while seeking to maintain aspects of the invention as a trade secret. Although the America Invents Act has since changed the law such that U.S. patents can no longer be invalidated for failure to comply with the best mode requirement, disclosure of the best mode is still required under U.S. patent law. Moreover, disclosure of the best mode arguably remains necessary for obtaining a patent with meaningful scope—for example, if details about the best mode are necessary to distinguish the invention from the prior art.

The very act of disclosing information in a patent application places a company at risk, particularly if the patent ultimately is not granted. Unless the company requests nonpublication and certifies that the invention has not been and will not be the subject of a patent application in another country (35 U.S.C. § 122), a patent application becomes a public record 18 months after the application has been filed. This means competitors will have access to the information contained in the patent application (and it is common practice for companies to monitor the patent applications filed by their competitors). If the patent ultimately is not granted, a company may lose some of its competitive edge by disclosing information about its invention without having been granted exclusivity over the invention.

Unlike patent protection, for which disclosure of the preferred host strain is required, trade secret protection enables a company to withhold access to its preferred host strain as a means of maintaining a competitive advantage. It is worth noting, however, that although the number of trade secret indictments brought by the U.S. attorney general is relatively low—only 17 cases in 2018, 4 of which had bioscience connections—the actual number of trade secret cases is much higher, and the vast majority of trade secret cases are civil litigation brought by the trade secret owners and not the U.S. Department of Justice. According to one law firm with offices across the United States and in Beijing, Shanghai, and Taipei, there are approximately 1,500 trade secret cases each year, many involving bioscience firms (Hodgson, 2019). Moreover, the damage to a biotechnology company from losing valuable trade secrets to a competitor can be profound; this is the case particularly for start-ups that may rely more heavily on trade secrets as a strategy for protecting valuable IP relative to larger, more established firms (Levine and Sichelman, 2018).

from other organizations, including foreign governments. The letter also invited research institutions to request briefings on these risks from FBI field offices. Concurrently, NIH privately reached out to grantee institutions with specific concerns; for example, NIH raised questions with the MD Anderson Cancer Center in Houston about three of its researchers, reported to be ethnic Chinese, who had reportedly failed to disclose foreign ties and had breached confidentiality (Tollefson, 2019; Zaveri, 2019). The Center moved to dismiss the three, two of whom chose to resign instead. And in early 2019, Emory University announced it had

fired two investigators who had failed to inform the university of their research affiliations with Chinese institutions (Tollefson, 2019). A similar notification from NIH was sent to Baylor College of Medicine regarding four faculty members. Rather than take steps to remove these faculty, the institution reviewed its policies and worked with the faculty to aid them in fully disclosing and describing their foreign collaborations (Ackerman, 2019). By June 2019, NIH had notified 61 institutions of apparent violations of rules concerning foreign relationships and had referred 16 cases to the U.S. Department of Health and Human Services' Inspector General (Mervis, 2019c).

Although these actions have involved Chinese researchers, and NIH has acknowledged that China has been a significant focus of investigation, officials at NIH and affected institutions maintain that these actions are not motivated by, and do not constitute, racial profiling. According to a senior NIH official, "we're focusing on objective behaviors. Not all of them involve China, and not all of the scientists whom we have discovered problems with are Chinese" (Tollefson, 2019). Nevertheless, the limited public detail behind these situations has given rise to concern among Chinese American and Chinese-origin researchers that the United States may not be a welcoming place for them (Tollefson, 2019).

Allegations by U.S. officials encompass several related issues that can be considered aspects of research misconduct, or the violation of academic norms or commitments: violations of the terms and conditions of federal grants that require disclosure of foreign financial conflicts and affiliations, unauthorized dissemination of proposals that have been circulated for confidential peer review, and theft of nonpublished research information (such as information obtained from the peer review of research manuscripts or through informal discussions).[25]

Disclosure of foreign financial conflicts is important, as described by the head of NIH's extramural research program, Michael Lauer, to prevent duplicative funding for the same research. Moreover, some Thousand Talents awards have required that IP developed in China remain in China and not be reported to U.S. institutions (Mervis, 2019b), conditions that might have affected NIH's willingness to fund the work in the first place or that could have prompted it to attach further conditions to its support.

Similarly, violation of confidentiality in peer review is a clear-cut violation of academic practices. Grant proposals contain a scientist's unique insights into how a problem can best be studied. They are circulated for review to experts in the same field who can understand the importance of the work and the feasibility of the proposed approach, and who conduct

[25]Two references describing norms of responsible research are NAS et al. (2009) and InterAcademy Partnership (2016).

these reviews confidentially to protect those insights from disclosure and possible application by competitors. Violating confidentiality is a violation of academic integrity regardless of who commits it, but such violations assume additional security and economic significance when they benefit scientists or economic interests in a competing nation. Additionally, some agencies, such as NIH, require that reviewers certify that they will not disclose grant information, and violations in those instances could therefore have legal ramifications.[26]

Theft or unauthorized disclosure of nonpublic information or IP from a proprietary (typically corporate) research institution is similarly conceptually clear-cut. Such institutions seek competitive advantage through their research efforts, and disclosure of research results or methods enables competitors to benefit from the same information without having to bear any of the associated costs. In an academic setting, however, disclosure of nonpublic information, such as prepublication scientific results, is more complicated. The ultimate objective of most academic research is full and open publication, not only of the research results but also of the methods used to obtain them, and at a level of detail sufficient to allow any suitably trained and equipped researcher to duplicate (and hence validate) those results. Universities and other fundamental research institutions exist to generate and share information while training the next generation of researchers in the process. All of those who graduate from academic institutions, or who leave one laboratory or job to join or found another, do so with the expectation that they will bring the expertise they have acquired in their previous position to their new one. So while they all have the obligation to protect unpublished or confidential information and to respect IP, the idea that foreign researchers who come to American universities will not leave with any knowledge and technology is not well reasoned. Moreover, foreign researchers are often members of U.S.-funded scientific teams and contribute their intellectual capital to their projects' success. Openness, engagement, and academic freedom have proven to be extremely effective in driving not just American scientific advances but American innovation—innovation that might have been stifled had the research been conducted under more restrictive conditions.

Even though the majority of unpublished research information is eventually disclosed, premature disclosure can give a head start to potential competitors, to the detriment of the originating laboratory. Moreover, some information associated with the research process may never be intended for publication. Again, violation of the academic obligation to respect the confidentiality of such information will harm American

[26]See https://grants.nih.gov/policy/research_integrity/confidentiality_peer_review.htm#prohibitions.

research, especially if it is being done—as is alleged by some U.S. officials—as a coordinated, systematic effort on the part of a competing nation (DOJ, 2018b; FBI, n.d.). If any individual is known to be violating these norms or is reasonably suspected of being likely to do so, action to mitigate that threat can be taken, whether by denying the individual an academic appointment, denying an appropriate visa, or removing the person from the research environment. Corrective action is much more difficult when a country may be suspected of fostering such activities among its nationals, but it is unclear who the specific offending parties may be. Blanket actions against—or scrutiny of—researchers solely on the basis of their nationality has the potential to degrade the openness that underlies the American research enterprise, and it can create the very "culture of suspicion" that MIT President Reif (2019) warned against.

Policies regarding foreign talent recruitment programs are challenged to find the appropriate balance. The first publicized U.S. government action against researchers engaged in foreign talent recruitment programs was taken by DOE in June 2019, when it issued a directive prohibiting DOE employees or contractors (including extramural researchers receiving DOE grants) from participating in the talent recruitment program of any country designated by DOE as a "foreign country of risk" (DOE, 2019). According to Under Secretary of Energy Paul Dabbar, "If you're working for [DOE], and taking taxpayer dollars, we don't want you to work for [foreign countries] at the same time" (Mervis, 2019a).

NIH appears to be taking a slightly different position. According to NIH Extramural Program Director Lauer, "Thousand Talents is not a threat [to the United States].... It's not the specific conduct we are focusing on, it's the failure to disclose it" (Mervis, 2019b). It is not clear whether the apparent discrepancy between the policies of DOE and NIH is merely a matter of how each policy is described, represents differences in agency views that remain to be harmonized, or stems from the differences in the missions of the two agencies and their security cultures.

This committee is not in a position to evaluate all of the risks of foreign engagement, since not all the details in such cases as those mentioned here are publicly known. Moreover, some types of alleged improper behavior that might fall under the rubric "academic espionage," when examined closely, appear to be an inherent consequence of openness, whereas others may require carefully balanced policy measures to address.

The committee does wish to acknowledge, as stated earlier in this chapter, that restrictions on foreign engagement at U.S. research institutions, even if deemed necessary, come at a price. Moreover, the perceptions generated by such actions can have serious consequences, particularly if not all of the underlying explanatory evidence can be made clear. Hence,

even if some direct harms can be attributed to inappropriate academic engagements such as those described here, the consequences of policy countermeasures may do more damage to the U.S. bioeconomy than the problem they are intended to solve. In congressional testimony on the importance of openness to U.S. education and research, former MIT President Charles Vest (2013) said he believed in the "leaky bucket theorem": when it comes to research and technology, "it is far more important to keep filling our bucket than it is to obsessively plug leaks."

In any event, any such policy instituted on the basis of a security perspective alone, without incorporating scientific and economic perspectives, risks being as one-sided as a policy instituted with no consideration of security at all. Given that science, economic, and security benefits are all at stake, a balanced policy process would involve all three.

State Involvement in Business Activities

An uneven international business landscape represents a substantial risk to the U.S. bioeconomy and puts U.S. companies at a disadvantage relative to some foreign competitors. For instance, the successful implementation of China's Made in China 2025 plan to transform that country into a world leader in 10 high-tech sectors, including biomedicine and high-performance medical instruments, by 2025 has the potential to disadvantage U.S. companies relative to their Chinese counterparts. According to the FBI, China plans to eliminate all foreign-produced technology in these sectors by 2025. A public document prepared by the FBI to educate the academic sector about the potential risks to academia states, "The Chinese government uses numerous methods—some legitimate but others, such as stealing technology from foreign competitors, meant to illicitly introduce foreign technology and knowledge to China" (FBI, n.d., p. 3). There are also a number of other reports and studies pointing to similar concerns (Brown et al., 2018; Morrison, 2019; U.S. Chamber of Commerce, 2017). According to the Office of the United States Trade Representative (USTR, 2018a), a state-directed economic program provides government subsidies for Chinese companies and mobilizes state-backed financial institutions to fund the acquisition of foreign biotech companies, with the goal of acquiring IP, and artificially distorts the market to establish Chinese companies as world leaders. An example is the $43 billion acquisition of Syngenta by the China National Chemical Corp. (ChemChina), a state-owned Chinese chemical company (Shields, 2017). The acquisition included Syngenta's entire U.S. business of more than 4,000 employees, 33 research sites, and 31 production and supply sites. The transaction was financed in part by a consortium of state-run financial entities. Critics

argue that state-directed investment on this scale undermines the principles of open trade and distorts global markets, prioritizing political considerations to the detriment of scientific innovation and normal economic incentives.

Under the 1988 Exon-Florio Amendment, as amended by the Foreign Investment Risk Review Modernization Act of 2018, the President has the power to block investments by foreign entities in U.S. companies or real estate when those investments may impair U.S. national security—for example, by putting technologies, data, or capabilities relevant to national security under foreign control.[27] In practice, the cabinet-level Committee on Foreign Investment in the United States (CFIUS) will try to work with parties to a transaction to mitigate any risk to national security. However, if the parties to the proposed transaction cannot reach an agreement on mitigation measures that satisfy the Committee, the Committee can recommend that the President block the transaction in its entirety. (The President also has the ability to reverse those types of transactions if they occurred without review and approval.) CFIUS was recently given extended authority to review transactions involving not just foreign ownership but also other investments that might afford foreign persons access to nonpublic technical information in the possession of certain U.S. businesses, along with any other "transaction, transfer, agreement, or arrangement designed to circumvent CFIUS."[28] Foreign investment controls may impose an economic price on particular firms by precluding them from accessing certain foreign sources of investment, but in the longer run they may advantage U.S. firms by slowing or preventing the loss of information or technology that can be used by foreign competitors.

Trade Barriers

The U.S. bioeconomy, like other aspects of the U.S. economy, relies on fair access to domestic and international markets for dissemination of products and services. Therefore, asymmetries in trade practices, such as regulatory approval processes for foreign products and forced

[27]On the U.S. Department of the Treasury website, see "Section 721 of the Defense Production Act of 1950, 50 USC App. 2170 (as amended by the Foreign Investment and National Security Act of 2007)," https://www.treasury.gov/resource-center/international/foreign-investment/Documents/Section-721-Amend.pdf; and "Summary of the Foreign Investment Risk Review Modernization Act of 2018," https://www.treasury.gov/resource-center/international/Documents/Summary-of-FIRRMA.pdf.

[28]See https://www.treasury.gov/resource-center/international/Documents/Summary-of-FIRRMA.pdf.

technology transfer practices, have the potential to hinder or harm the U.S. bioeconomy.

Asymmetric Regulatory Practices

Asymmetric regulatory practices between trading partners have the potential to affect the ability of domestic companies to reach foreign markets. With respect to the bioeconomy, this is particularly the case for agricultural biotechnology and the pharmaceutical sector. If applicable regulations for a given product are not harmonized among major global markets, innovations from one nation will have difficulty gaining full or timely reach into the global bioeconomy. And when different countries or trade blocks take philosophically different approaches to regulation, as do the United States, with its largely product-based regulatory system, and the European Union, with its more process-based system, the problem is not just that products will obtain different regulatory approvals at different times in different jurisdictions, but that products regulated in one jurisdiction may be completely unregulated in another.

The United States generally aspires to regulate new crops improved through biotechnology under a risk-based, science-based framework that treats products according to the risks they pose, independent of the process by which they were generated. The European Union takes a precautionary approach in which genetically modified crops must undergo risk analyses not required for unmodified crops. In 2003, the United States filed a complaint with the World Trade Organization (WTO) claiming that the European Union's de facto moratorium on the approval of genetically modified crop imports violated WTO agreements (Chereau, 2014). In 2006, WTO ruled that this moratorium and the genetically modified organism (GMO) approval processes of several European Union states were illegal. In 2013, the European Union General Court ruled that the European Union must process a long-pending authorization to import a genetically modified corn (Law Library of Congress, 2014). However, a number of European states continue to oppose the decision.

The United States considers the European Union's GMO approval policies to be inconsistent with a risk-based approach to the regulation of agriculture, and it regards the WTO ruling as confirmation that these policies constitute an unwarranted barrier to trade. The United States views the policies not only as denying access to markets in the European Union but also denying U.S. companies access to markets in other countries (outside of the European Union) that fear they will not be able to export the resulting crops to the European Union.

Another example within the agricultural sector, although with very different implications, relates to the more permissive regulatory environment for gene-edited livestock. In 2008, FDA issued guidance stating that it would regulate genetically engineered animals under the Federal Food, Drug, and Cosmetic Act. FDA considered the use of the recombinant DNA used to create the genetic modification to represent a "new animal drug," and therefore subject to "government review and approval, the same as a veterinary drug such as an antibiotic or pain reliever" (Miller and Cohrssen, 2018). This guidance and the subsequent requirements for labeling led to an 11-year-long regulatory review and labeling decision-making process for a genetically engineered salmon (Clayton, 2019). As a result, other American companies and researchers working on gene editing of other animal species for food (such as hornless cattle, heat-resistant cattle, goats with an antimicrobial protein in their milk, and disease-resistant pigs) have decided to move their research and production to Argentina, Australia, Brazil, and Canada (Ledford, 2019). In short, the implications of the slow and uncertain regulatory process are causing some American companies to move overseas, thus potentially leaving the United States behind.

There is also a lack of reciprocity with respect to pharmaceutical licensing. The regulatory rules for approval of pharmaceuticals in China are opaque, and decisions to approve are based on factors other than science. For example, if a U.S. drug company wants to license a drug in China, it must complete the approval process in the United States before it can begin the approval process in China, whereas other countries allow for concurrent clinical trials. This practice limits the time that a U.S. drug company can market a patented drug in China.

Forced Technology Transfer

China's noncompliance with some international business norms and WTO rules, particularly with respect to forced technology transfer, have been documented by USTR (2018b). According to the USTR report, the Chinese government forces the transfer of foreign companies' technologies and IP to Chinese companies though opaque administrative licensing and approval processes, noting that "Chinese officials may use oral communication and administrative guidance to pressure foreign firms to transfer technology." Such policies clearly disadvantage U.S. firms relative to Chinese firms, which face no such barrier selling products in the United States. The USTR's 2018 report to Congress on China's WTO compliance, issued in February 2019, observes that, "despite repeated commitments to refrain from forcible technology transfer from U.S. companies,

China continues to do so through market access restrictions, the abuse of administrative processes, licensing regulations, asset purchases, cyber and physical theft" (USTR, 2019).

The Bioeconomy as a Component of Critical Infrastructure

In the United States, critical infrastructures include the financial sector, the electrical power grid, transportation systems, energy systems, communications systems, and a range of others.[29] To the extent that the bioeconomy becomes increasingly integrated into these critical infrastructures, incapacitation or failure of key bioeconomy facilities or services could also threaten security, public health, or public safety. For example, the production of vaccines for public health could be considered part of the critical health care and public health infrastructure. Foods, fuels, and medicine can all be considered critical to the nation's health and stability. Therefore, to the extent that they are produced on automated and digital biotech platforms, their cyber and other vulnerabilities need to be recognized and specifically addressed.

Incapacitation of critical facilities need not, however, require a natural disaster or a physical or cyberattack. The operation of any bioeconomy facility that is dependent on input materials available only overseas is subject to interruption if the supply chains for those inputs are interrupted, whether by decisions of foreign powers to withhold shipment or by failures of international transportation networks.[30] Moreover, dependence on imports exposes the United States to potential sources of counterfeit or adulterated products if the regime ensuring product integrity in the supplier country is inadequate.[31] Protecting against such interruptions requires developing multiple secure sources of supply for critical inputs, stockpiling the inputs, or engineering around these dependencies.

[29]Presidential Policy Directive 21, "Critical Infrastructure Security and Resilience" (White House Office of the Press Secretary, 2013), see footnote 23.

[30]Note that "supply chain" in this discussion refers to the routes by which the materials and components necessary to produce some output of the bioeconomy are integrated into final products or used in delivering services. This meaning is different from the phrase's use in "supply chain attacks," as discussed in the section on cybersecurity, which refers to engineering flaws into component systems with the expectation that those components would be incorporated in more complicated systems that could then be penetrated by exploiting those flaws.

[31]In 2008, for example, 81 deaths were associated with contaminated supplies of the blood thinner heparin produced by 12 Chinese companies and exported to 11 countries. The companies apparently all drew on supplies of an active ingredient contaminated with a chemical that was difficult to distinguish from heparin but was much cheaper (Greenemeier, 2008; Harris, 2008; Powell, 2008).

Traditional Biosecurity and Biosafety Risks

The tools of today's bioeconomy are enabling new capabilities that can generate concerns regarding traditional biothreats, which encompass primarily those pathogens considered to be most dangerous and lethal or used as weapons in the past. These agents were placed on security lists, such as the Federal Select Agent List, to protect against their unauthorized acquisition, possession, and use.[32] Cold War–era bioweaponeers wanted to alter pathogens to make them deadlier, to spread more easily, or able to evade diagnosis and treatment, but these goals required heavy investment, expertise, and time commitment and faced knowledge and technical barriers. With today's tools, however, the acquisition of dangerous pathogenic organisms can be facilitated through synthetic creation "from scratch" based on their known genomic sequences, and DNA is commercially available from a growing number of gene synthesis companies throughout the world. Recent examples include reconstruction of such viruses as polio (Cello et al., 2002), the 1918 influenza virus (Tumpey et al., 2005), and most recently horsepox (Noyce et al., 2018). Such developments as the efficient genome editor CRISPR illustrate the programmable tools that could rewrite genetic code to alter pathogens in ways aspired to by weapons programs of the past. Another possibility is the creation of novel bioweapons that do not currently exist on any security control lists and would be difficult to prevent, detect, and treat. A 2018 study by the National Academies highlights the most concerning capabilities stemming from synthetic biology that could harm humans (NASEM, 2018a).

Although manipulation of pathogenic organisms remains technically challenging, then, the tools of today's biotechnology could lower the technological barriers (DiEuliis, 2019). A strong bioeconomy will also pursue the ability to manipulate biological organisms, the same capabilities that could drive bioweapons programs, albeit for different intentions and with different organisms. It remains to be seen whether expansion of the knowledge base and specialized tools for bioeconomic products, such as the open-source biology movement, can also serve in similar kinds of manipulations of pathogens (Cohn, 2005). Presumably, these capabilities will require tailored bioinformatics, which may also be applicable to making or tinkering with harmful pathogens if made broadly available (i.e., not protected as IP within companies).

[32]The Federal Select Agent Program regulates the possession, transport, and use of certain biological pathogens that are considered to pose a severe threat to public, animal, or plant health or safety. This program and the agents it regulates are described at www.selectagents.gov.

It is important to note that, while growing pathogens to scale, storing them stably, and delivering them to target populations are the most challenging aspects of bioweapon development, some of these capabilities are real and purposeful goals of the bioeconomy—to scale up production of organisms that can produce high-value products or themselves be used as products. As industry continues to resolve challenges in the creation of chemicals, there is also a growing overlap between biological and chemical weapons. Importantly, biothreats to humans are only one component of the risk; threats to animals, plants, agriculture, the environment, and materials are also of concern. While these potential enablers of biothreats cannot and should not be minimized, strong public health and animal health infrastructures will still serve as robust primary defenses.

Certain U.S. export controls serve as one means of countering some biosecurity concerns. For national security or foreign policy purposes, the U.S. government requires that licenses be obtained for the export of some goods, technology, and information to certain destinations to prevent their falling into the hands of adversaries. Moreover, communication of controlled technical information within the United States to a foreign national is deemed an export to that individual's country, and may require an export license as well. Fundamental research—defined broadly as research intended to be openly published—is not subject to export controls, but such controls may apply to information that is protected as proprietary or is otherwise not public.

Export controls may have the effect of preventing entities abroad from acquiring technology that could allow them to compete with U.S firms. It is important to note, however, that these controls can serve to protect national security at the expense of competitiveness, because U.S. firms may be precluded from selling products to certain foreign customers, and foreign manufacturers may have an incentive to avoid the use of U.S. components to prevent triggering the imposition of U.S. export controls.

Almost all bioeconomy-related items that are subject to export controls fall under the Export Administration Regulations (EAR), which establish export controls on so-called "dual-use" items, which as noted earlier are commercial items that can also be used for military or terrorist purposes.[33] The U.S. Department of Commerce's Bureau of Industry and Security administers the EAR, which include the Commerce Control List that

[33]The term "dual-use" also describes research done for legitimate purposes that can be misused for harm, but that definition is not relevant to export controls.

describes items subject to dual-use controls.[34] Because controls on goods by one country can be undercut if other exporting countries do not control the same items, nations work together to coordinate and harmonize their export control systems. Controls on items related to chemical and biological weapons are coordinated informally (i.e., in the absence of a formal mechanism such as a treaty) through the Australia Group. Australia Group members meet periodically to consider changes to the list of controlled items. The United States also has the ability to control items unilaterally.

Under a provision in the National Defense Authorization Act of 2019, Congress called for the U.S. Department of Commerce to establish export controls on emerging and foundational technologies that are "essential to the national security of the United States." This process is intended to take into account the status of development of these technologies in foreign countries, the effect such controls might have on their development in the United States, and the potential effectiveness of the controls in curbing the proliferation of these technologies.[35] On November 19, 2018, the U.S. Department of Commerce issued an Advance Notice of Proposed Rulemaking (ANPRM) in the *Federal Register* to solicit public comment on how emerging technologies could be identified and assessed for the purpose of updating export control lists.[36] The ANPRM asked in particular about whether biotechnology should be considered for controls, and also reiterated that the Department does not seek to expand export controls into areas not currently subject to them, such as fundamental research.

Even with this qualification, many respondents to the ANPRM warned that instituting controls not precisely targeting specific technological developments would harm the United States' ability to develop emerging technologies. A consortium of academic organizations warned that "overly broad or vague controls will result in unnecessary regulations that will stifle scientific progress and impede research."[37] The Biotechnology Innovation Organization cautioned the Department to "move with extreme caution to avoid unintended harm to U.S. domestic research and development of novel biotechnologies, U.S. international competitiveness,

[34]A separate system of export controls, run by the U.S. Department of State, governs the export of weapons systems and military-specific technologies. This system, administered as the International Trafficking in Arms Regulations, is less relevant to the bioeconomy.

[35]National Defense Authorization Act of 2018, P.L. 115-232, § 1758(a)(1).

[36]U.S. Department of Commerce, 2018. Foundational technologies are to be addressed in a subsequent ANPRM.

[37]Letter to the U.S. Department of Commerce from the Council on Governmental Relations, the Association of American Universities, the Association of Public and Land-grant Universities, the American Council on Education, and the AAMC (formerly the Association of American Medical Colleges), January 10, 2019, available at https://www.regulations.gov/document?D=BIS-2018-0024-0140.

and economic growth," pointing out that the biotechnology industry is an inherently global ecosystem and utilizes global clinical research partnerships.[38] The U.S. Department of Commerce received 247 responses to its request for comment and as of this writing had not responded to them.

Risks from Global Climate Change

Global climate change will significantly affect the bioeconomy even as the bioeconomy provides means to help offset greenhouse gas emissions by providing a biobased pathway for the creation of products that are currently dependent on fossil fuels (such as petroleum-based plastics). Food and feed crops, lignocellulosic bioenergy crops, and crops grown for plant-derived sugars as feedstock for fermentative processing are susceptible to temperature and water stresses, and they will be vulnerable to insects and pathogens that migrate from their current habitats. The government's forecast on the impacts of climate change on agriculture states that the largest contributing factor to declines in U.S. agricultural productivity will be increases in temperature during the growing season in the Midwest (USGCRP, 2018). Arresting climate change–induced declines in agricultural productivity will require improvements in three dimensions—quality, yield, and an optimized and sustainable system that does not compromise benefits of the system. Moreover, while some crops, such as grain and biomass sorghum, may be able to withstand climate change–induced stresses such as drought, for most species, mitigation will require identifying more resilient genotypes from among naturally occurring diversity, engineering them for greater resilience, or moving crop cultivation to areas that replicate the climate in which they are currently grown (which has obvious geographic and land-use implications).

While global climate change is an existential threat that specifically affects agricultural production at the foundation of the bioeconomy, partial mitigation can be accomplished through long-term and strategic support of a vibrant bioeconomy as discussed in the recommendations in this report.

CONCLUSIONS

This chapter reviewed the risks identified by the committee that have the potential to adversely affect the U.S. bioeconomy. Where possible, the committee has discussed some of the policy tools that can be used to

[38]Letter to the U.S. Department of Commerce from the Biotechnology Innovation Organization, January 10, 2019, available at https://www.regulations.gov/document?D=BIS-2018-0024-0137.

mitigate these risks. It is important to recognize that some of the identified policy actions have the potential to cause unintended consequences or outcomes. This potential is best illustrated by, but is not limited to, the concerns around foreign researchers or the regulatory system. Over the course of its deliberations, the committee arrived at a number of conclusions related to the risks facing to the U.S. bioeconomy.

Conclusion 7-1: Limitations on fundamental research, whether through a lack of support, the implementation of restrictive research regulations, or the inability to develop and attract a skilled workforce, could erode the United States' ability to produce breakthrough scientific results and develop enabling technologies.

Conclusion 7-2: Access to data is vital to the bioeconomy research enterprise, and issues related to data sharing (domestically or internationally), benefit sharing, or the potential use of data for malicious reasons will require carefully considered solutions.

Conclusion 7-3: The bioeconomy faces many of the traditional cybersecurity risks faced by other sectors. Common features of the bioeconomy that pose potential vulnerabilities include reliance on open-source software, large and potentially sensitive datasets, and communication through the Internet (such as via networked devices that are potentially running outdated software).

Conclusion 7-4: Concerns about foreign researchers, potential policy actions to address those concerns, and the perceptions generated by such actions have the potential to adversely affect the bioeconomy if not informed by input from the scientific community. Given that science, economic, and security benefits are all at stake, a balanced policy process would involve all three perspectives.

Conclusion 7-5: More information is needed to understand the impact of current and proposed requirements for patent eligibility on the sustainability and growth of the U.S. bioeconomy. Specifically, more information is needed regarding the extent to which patent eligibility requirements impact the ability of start-up companies and larger, well-established companies to secure patent protection in the United States, and whether these companies are more or less inclined toward or successful in securing patent protection internationally.

Conclusion 7-6: International asymmetries regarding the regulation of bioeconomy products, data-sharing agreements and practices,

and industrial mergers and acquisitions (including associated technology transfers and potential state involvement) are risks to the U.S. bioeconomy.

The discussion of risks and potential policy responses in this chapter has stressed the importance of finding the right balance between protecting the U.S. research enterprise and the safety of bioeconomy products, on the one hand, and not unduly impeding innovation in and the growth of the bioeconomy on the other. This issue is addressed further in the next chapter, which presents the committee's overarching conclusions and recommendations.

REFERENCES

Aboy, M., J. Liddicoat, K. Liddell, M. Jordan, and C. Crespo. 2017. After *Myriad*, what makes a gene patent claim "markedly different" from nature? *Nature Biotechnology* 35(9):820–825.

Aboy, M., C. Crespo, K. Liddell, J. Liddicoat, and M. Jordan. 2018. Was the *Myriad* decision a "surgical strike" on isolated DNA patents, or does it have wider impacts? *Nature Biotechnology* 36(12):1146–1149.

Aboy, C., K. Liddell, T. Minssen, and J. Liddicoat. 2019. *Mayo*'s impact on patent applications related to biotechnology, diagnostics and personalized medicine. *Nature Biotechnology* 37(5):513–518.

Ackerman, T. 2019. MD Anderson ousts 3 scientists over concerns about Chinese conflicts of interest. *Houston Chronicle*, April 20. https://www.houstonchronicle.com/news/houston-texas/houston/article/MD-Anderson-fires-3-scientists-over-concerns-13780570.php (accessed September 5, 2019).

Al-Rubaie, M., and J. Chang. 2018. *Privacy preserving machine learning: Threats and solutions.* http://www.eng.usf.edu/~chang5/papers/19/SP_mohammad_19.pdf (accessed October 19, 2019).

Aldhous, P. 2019. This genealogy database helped solve dozens of crimes. But its new privacy rules will restrict access by cops. *BuzzFeedNews*, May 19. https://www.buzzfeednews.com/article/peteraldhous/this-genealogy-database-helped-solve-dozens-of-crimes-but (accessed October 16, 2019).

Arkin, A. P., R. W Cottingham, C. S Henry, N. L. Harris, R. L. Stevens, S. Maslov, P. Dehal, D.Ware, F. Perez, S. Canon, et al. 2018. KBase: The United States Department of Energy systems biology knowledgebase. *Nature Biotechnology* 36:566–569.

Armstrong, R. E., M. D. Drapeau, C. A. Loeb, J. J. Valdes, eds. 2010. *Bio-inspired innovation and national security.* Washington, DC: National Defense University.

Audretsch, D. B., and M. P. Feldman. 1996. Innovative clusters and the industry life cycle. *Review of Industrial Organization* 11(2):253–273.

Bahr, R. W. 2016. *Formulating a subject matter eligibility rejection and evaluating the applicant's response to a subject matter eligibility rejection*. Alexandria, VA: U.S. Patent and Trademark Office. https://www.uspto.gov/sites/default/files/documents/ieg-may-2016-memo.pdf (accessed October 19, 2019).

Bahr, R. W. 2018a. *Changes in examination procedure pertaining to subject matter eligibility, recent subject matter eligibility decision (Berkheimer v. HP, Inc.).* Alexandria, VA: U.S. Patent and Trademark Office. https://www.uspto.gov/sites/default/files/documents/memo-berkheimer-20180419.PDF (accessed October 19, 2019).

Bahr, R. W. 2018b. *Recent subject matter eligibility decision: Vanda Pharmaceuticals Inc. v. West-Ward Pharmaceuticals.* Alexandria, VA: U.S. Patent and Trademark Office. https://www.uspto.gov/sites/default/files/documents/memo-vanda-20180607.PDF (accessed October 19, 2019).

Bailey, M. N., and N. Montalbano. 2017. *Clusters and innovation districts: Lessons from the United States experience.* Washington, DC: Brookings Institution. https://www.brookings.edu/wp-content/uploads/2017/12/es_20171208_bailyclustersandinnovation.pdf (accessed September 5, 2019).

Bavasi, H., L. Thornton, D. Peloquin, and M. Barnes. 2017. Using biospecimens collected abroad in future research: Key considerations. *Medical Research Law & Policy Report*. U.S. Bureau of National Affairs. https://www.ropesgray.com/~/media/Files/articles/2017/April/Bloomberg%20BNA%20Biospecimens%20Abroad%20for%20Research%20Article%204-19-17.ashx (accessed May 23, 2019).

Black, P. E., L. Badger, B. Guttman, and E. Fong. 2016. *Dramatically reducing software vulnerabilities: Report to the White House Office of Science and Technology Policy*. NISTIR 8151. https://nvlpubs.nist.gov/nistpubs/ir/2016/NIST.IR.8151.pdf (accessed September 5, 2019).

Braudt, D. B. 2018. Sociogenomics in the 21st century: An introduction to the history and potential of genetically-informed social science. *Sociology Compass* 12(10):e12626. doi: 10.1111/soc4.12626.

Broniatowski, D. A., A. M. Jamison, S. Qi, L. AlKulaib, T. Chen, A. Benton, S. C. Quinn, and M. Dredze. 2018. Weaponized health communication: Twitter bots and Russian trolls amplify the vaccine debate. *American Journal of Public Health* 108(10):1378–1384. doi: 10.2105/AJPH.2018.304567.

Brown, M., and P. Singh. 2018. *China's technology transfer strategy*. https://admin.govexec.com/media/diux_chinatechnologytransferstudy_jan_2018_(1).pdf (accessed October 16, 2019).

Cancer Genome Atlas Research Network. 2013. The cancer genome atlas pan-cancer analysis project. *Nature Genetics* 45:1113. doi: 10.1038/ng.2764.

CDC and USDA (U.S. Centers for Disease Control and Prevention and U.S. Department of Agriculture). 2017a. *Information systems security controls guidance*. https://www.selectagents.gov/resources/Information_Systems_Guidance.pdf (accessed September 5, 2019).

CDC and USDA. 2017b. *Security plan guidance.* https://www.selectagents.gov/resources/Security_Plan_Guidance.pdf (accessed September 5, 2019).

Cello, J., A. V. Paul, and E. Wimmer. 2002. Chemical synthesis of poliovirus cDNA: Generation of infectious virus in the absence of natural template. *Science* 297(5583):1016–1018.

Chao, B., and A. Mapes. 2016. An early look at *Mayo*'s impact on personalized medicine. *Patently-O Patent Law Journal* 10:10–14.

Chereau, C. J. 2014. Biotechnology: Can the transatlantic trade and investment partnership reconcile EU and U.S. differences on GMOs? *International Journal of Trade and Global Markets* 7(4):316–338.

Clayton, C. 2019. AquaBounty salmon no longer swimming up regulatory stream. *Ag Policy Blog*, July 11. https://www.dtnpf.com/agriculture/web/ag/blogs/ag-policy-blog/blog-post/2019/07/11/aquabounty-salmon-longer-swimming-2 (accessed October 19, 2019).

Cohen, J. 2018. A chat with the geneticist who predicted how the police may have tracked down the Golden State Killer. *Science News*, April 29. https://www.sciencemag.org/news/2018/04/chat-geneticist-who-predicted-how-police-may-have-tracked-down-golden-state-killer (accessed October 16, 2019).

Cohn, D. 2005. Open-source biology evolves. *Wired*, January 17. https://www.wired.com/2005/01/open-source-biology-evolves (accessed September 5, 2019).

Comfort, N. 2018. Sociogenomics is opening a new door to eugenics. *MIT Technology Review*, October 23. https://www.technologyreview.com/s/612275/sociogenomics-is-opening-a-new-door-to-eugenics (accessed October 16, 2019).

Council of Economic Advisors. 2018. *The cost of malicious cyber activity to the U.S. economy*. https://www.whitehouse.gov/wp-content/uploads/2018/03/The-Cost-of-Malicious-Cyber-Activity-to-the-U.S.-Economy.pdf (accessed August 9, 2019).

CSIS (Center for Strategic and International Studies). 2005. Security controls on the access of foreign scientists and engineers to the United States. https://www.csis.org/analysis/security-controls-access-foreign-scientists-and-engineers-united-states (accessed June 9, 2019).

Dankar, F. K., A. Ptitsyn, and S. K. Dankar. 2018. The development of large-scale de-identified biomedical databases in the age of genomics—principles and challenges. *Human Genomics* 12(1):19. doi: 10.1186/s40246-018-0147-5.

Dhar, D., and J. H.-E. Ho. 2009. Stem cell research policies around the world. *Yale Journal of Biology and Medicine* 82(3):113–115.

DiEuliis, D. 2018. Biotechnology for the battlefield: In need of a strategy. *War on the rocks*, November 27. https://warontherocks.com/2018/11/biotechnology-for-the-battlefield-in-need-of-a-strategy (accessed July 2, 2019).

DiEuliis, D. 2019. Key national security questions for the future of synthetic biology. *Fletcher Forum of World Affairs* 43(1):1.

DOE (U.S. Department of Energy). 2019. *Department of Energy foreign government talent recruitment programs*. DOE Order O 486.1. https://www.energy.gov/sites/prod/files/2019/06/f63/DOE%20O%20486.1.pdf (accessed June 18, 2019).

DOJ (U.S. Department of Justice). 2018a. *Chinese scientist sentenced to prison in theft of engineered rice.* https://www.justice.gov/opa/pr/chinese-scientist-sentenced-prison-theft-engineered-rice (accessed September 6, 2019).

DOJ. 2018b. *Statement of E. W. Priestap, Assistant Director, Counterintelligence Division, Federal Bureau of Investigation, before the Committee on the Judiciary, Subcommittee on Border Security and Immigration, U.S. Senate, at a hearing "Student Visa Integrity: Protecting Educational Opportunity and National Security,"* June 6. https://www.judiciary.senate.gov/imo/media/doc/06-06-18%20Priestap%20Testimony.pdf (accessed October 16, 2019).

DOJ. 2019. *Interim policy: Forensic genetic genealogical DNA analysis and searching*. https://www.justice.gov/olp/page/file/1204386/download (accessed October 16, 2019).

DOJ Office of Public Affairs. 2019. *Department of Justice announces interim policy on emerging method to generate leads for unsolved violent crimes*. Press release 19-1017. https://www.justice.gov/opa/pr/department-justice-announces-interim-policy-emerging-method-generate-leads-unsolved-violent (accessed October 16, 2019).

EBRC (Engineering Biology Research Consortium). 2019. *Engineering biology: A research roadmap for the next-generation bioeconomy*. https://roadmap.ebrc.org (accessed July 3, 2019).

Ellis, S. 2018. U.S. biopharma firms hit by cyber attacks from China. *Bioworld.* http://www.bioworld.com/content/us-biopharma-firms-hit-cyber-attacks-china-0 (accessed November 9, 2019).

Erlich, Y., T. Shor, I. Pe'er, and S. Carmi. 2018. Identity inference of genomic data using long-range familial searches. *Science* 362(6415):690–694.

FBI (Federal Bureau of Investigation). n.d. *China: The risk to academia*. https://www.research.psu.edu/sites/default/files/FBI_Risks_To_Academia.pdf (accessed August 12, 2019).

Feldman, M. P., and N. Massard, eds. 2002. *Institutions and systems in the geography of innovation.* New York: Kluwer Academic Publishers.

Fiume, M., M. Cupak S. Keenan, J. Rambla, S. de la Torre, S. O. M. Dyke, A. J. Brookes, K. Carey, D. Lloyd, P. Goodhand, M. Haeussler, M. Baudis, H. Stockinger, L. Dolman, I. Lappalainen, J. L. Törnroos, J. D. Spalding, S. Ur-Rehman, A. Page, P. Flicek, S. Sherry, D. Haussler, S. Varma, G. Saunders, and S. Scollen. 2019. Federated discovery and sharing of genomic data using Beacons. *Nature Biotechnology* 37(3):220–224.

Flach, J., C. S. Ribeiro, M. B. van der Waal, R. X. van der Waal, E. Claassen, L. H. M. van de Burgwal. 2019. The Nagoya protocol on access to genetic resources and benefit sharing: Best practices for users of lactic acid bacteria. *PharmaNutrition* 9:100158. doi: 10.1016/j.phanu.2019.100158.

Fredrikson, M., E. Lantz, S. Jha, S. Lin, D. Page, and T. Ristenpart. 2014. *Privacy in pharmacogenetics: An end-to-end case study of personalized warfarin dosing*. San Diego, CA: USENIX Association. https://www.usenix.org/system/files/conference/usenixsecurity14/sec14-paper-fredrikson-privacy.pdf (accessed October 19, 2019).

Galdzicki, M., C. Rodriguez, D. Chandran, H. M. Sauro, and J. H. Gennari. 2011. Standard biological parts knowledgebase. *PLoS One* 6(2):e17005. doi: 10.1371/journal.pone.0017005.

Greenemeier, L. 2008. Heparin scare: Deaths from tainted blood-thinner spur race for safe replacement. *Scientific American*, November 4. https://www.scientificamerican.com/article/heparin-scare-deaths (accessed September 5, 2019).

Gryphon Scientific and Rhodium Group. 2019. *China's biotechnology development: The role of U.S. and other foreign engagement: A report prepared for the U.S.-China Economic and Security Review Commission*. https://www.uscc.gov/sites/default/files/Research/US-China%20Biotech%20Report.pdf (accessed July 1, 2019).

Guhr, A., S. Kobold, S. Seltmann, A. E. M. Seiler Wulczyn, A. Kurtz, and P. Löser. 2018. Recent trends in research with human pluripotent stem cells: Impact of research and use of cell lines in experimental research and clinical trials. *Stem Cell Reports* 11(2):485–496. doi: 10.1016/j.stemcr.2018.06.012.

Harris, G. 2008. U.S. identifies tainted heparin in 11 countries. *The New York Times*, April 22. https://www.nytimes.com/2008/04/22/health/policy/22fda.html (accessed July 5, 2019).

Hiemstra, S. J., M. Brink, and T. van Hintum. 2019. *Digital Sequence Information (DSI): Options and impact of regulating access and benefit sharing—stakeholder perspectives*. CGN Report 42. Wageningen, Netherlands: Wageningen University & Research. https://library.wur.nl/WebQuery/wurpubs/fulltext/470286 (accessed September 5, 2019).

Hiscox. 2018. *Small Business Cyber Risk Report™*. https://www.hiscox.com/documents/2018-Hiscox-Small-Business-Cyber-Risk-Report.pdf (accessed October 16, 2019).

Hodgson, J. 2019. Genentech trade secrets theft highlights risk for biotechs. *Nature Biotechnology* 37(1):9–10.

Hyde, C. L., M. W. Nagle, C. Tian, X. Chen, S. A. Paciga, J. R. Wendland, J. Y. Tung, D. A. Hinds, R. H. Perlis, and A. R. Winslow. 2016. Identification of 15 genetic loci associated with risk of major depression in individuals of European descent. *Nature Genetics* 48(9):1031–1036. doi: 10.1038/ng.3623.

Ilic, D., and C. Ogilvie. 2017. Concise review: Human embryonic stem cells—What have we done? What are we doing? Where are we going? *Stem Cells* 35(1):17–25. doi: 10.1002/stem.2450.

InterAcademy Partnership. 2016. *Doing global science: A guide to responsible conduct in the global research enterprise*. Princeton, NJ: Princeton University Press. https://www.interacademies.org/33345/Doing-Global-Science-A-Guide-to-Responsible-Conduct-in-the-Global-Research-Enterprise (accessed October 19, 2019).

IOM (Institute of Medicine). 2012. *Adverse effects of vaccines: Evidence and causality*. Washington, DC: The National Academies Press. https://doi.org/10.17226/13164.

Jefferson, O. A., D. Köllhofer, T. H. Ehrich, and R. A. Jefferson. 2015. Gene patent practice across plant and human genomes. *Nature Biotechnology* 33(10):1033–1038.

Jouvenal, J. 2018. To find alleged Golden State Killer, investigators first found his great-great-great-grandparents. *The Washington Post*, April 30. https://www.washingtonpost.com/local/public-safety/to-find-alleged-golden-state-killer-investigators-first-found-his-great-great-great-grandparents/2018/04/30/3c865fe7-dfcc-4a0e-b6b2-0bec548d501f_story.html (accessed October 16, 2019).

Kaiser, J. 2018. We will find you: DNA search used to nab Golden State Killer can home in on about 60% of white Americans. *Science News*, October 11. https://www.sciencemag.org/news/2018/10/we-will-find-you-dna-search-used-nab-golden-state-killer-can-home-about-60-white (accessed October 15, 2019).

Laestadius, L. I., J. R. Rich, and P. L. Auer. 2017. All your data (effectively) belong to us: Data practices among direct-to-consumer genetic testing firms. *Genetics in Medicine* 19(5):513–520.

Lai, H.-E., C. Canavan, L. Cameron, S. Moore, M. Danchenko, T. Kuiken, Z. Sekeyová, and P. S. Freemont. 2019. Synthetic biology and the United Nations. *Trends in Biotechnology* 37(11):1146–1151. https://www.sciencedirect.com/science/article/pii/S0167779919301337 (accessed September 5, 2019).

Law Library of Congress. 2014. *Restrictions on genetically modified organisms*. https://www.loc.gov/law/help/restrictions-on-gmos/restrictions-on-gmos.pdf (accessed June 17, 2019).

Le Feuvre, R. A., and N. S. Scrutton. 2018. A living foundry for synthetic biological materials: A synthetic biology roadmap to new advanced materials. *Synthetic and Systems Biotechnology* 3(2):105–112. doi: 10.1016/j.synbio.2018.04.002.

Ledford, H. 2019. Gene-edited animal creators look beyond U.S. market. *Nature* 566:433–434. doi: 10.1038/d41586-019-00600-4.

Levine, D. S., and T. Sichelman. 2018. Why do startups use trade secrets? *Notre Dame Law Review* 94(2):751–820.

Majumder, M. A. 2018. United States: Law and policy concerning transfer of genomic data to third countries. *Human Genetics* 137(8):647–655. doi: 10.1007/s00439-018-1917-9.

Mantle, J. L., J. Rammohan, E. F. Romantseva, J. T. Welch, L. R. Kauffman, J. McCarthy, J. Schiel, J. C. Baker, E. A. Strychalski, K. C. Rogers, and K. H. Lee. 2019. Cyberbiosecurity for biopharmaceutical products. *Frontiers in Bioengineering and Biotechnology* 7:116. doi: 10.3389/fbioe.2019.00116.

Martin, C. 2018. Privacy and consumer genetic testing don't always mix. *Science News*, June 5. https://www.sciencenews.org/blog/science-public/privacy-and-consumer-genetic-testing-dont-always-mix (accessed October 16, 2019).

Mervis, J. 2019a. DOE to limit foreign research collaborations. *Science* 363(6428):675–676.

Mervis, J. 2019b. NIH probe of foreign ties has led to undisclosed firings—and refunds from institutions. *Science*, June 26. https://www.sciencemag.org/news/2019/06/nih-probe-foreign-ties-has-led-undisclosed-firings-and-refunds-institutions (accessed August 12, 2019).

Mervis, J. 2019c. Powerful U.S. senator calls for vetting NIH grantees at hearing on foreign influences. *Science*, June 6. https://www.sciencemag.org/news/2019/06/powerful-us-senator-calls-vetting-nih-grantees-hearing-foreign-influences (accessed August 12, 2019).

Miller, H. I., and J. J. Cohrssen. 2018. FDA overreach on genetically engineered animals. *Issues in Science and Technology* 34(3).

Millett, P., T. Binz, S. W. Evans, T. Kuiken, K. Oye, M. J. Palmer. C. van der Vlugt, K. Yambao, and S. Yu. 2019. Developing a comprehensive, adaptive, and international biosafety and biosecurity program for advanced biotechnology: The iGEM experience. *Applied Biosafety* 24(2):64–71. doi: 10.1177/1535676019838075.

Monteiro, R. L. 2018. The new Brazilian General Data Protection Law—a detailed analysis. *IAPP*, August 15. https://iapp.org/news/a/the-new-brazilian-general-data-protection-law-a-detailed-analysis (accessed September 6, 2019).

Morrison, W. 2019. Enforcing U.S. trade laws: Section 301 and China. Congressional Research Service "In Focus" IF10708, updated June 26, 2019. https://fas.org/sgp/crs/row/IF10708.pdf (accessed October 1, 2019).

Murch, R. S., W. K. So, W. G. Buchholz, S. Raman, and J. Peccoud. 2018. Cyberbiosecurity: An emerging new discipline to help safeguard the bioeconomy. *Frontiers in Bioengineering and Biotechnology* 6:39. doi: 10.3389/fbioe.2018.00039.

NAS, NAE, and IOM (National Academy of Sciences, National Academy of Engineering, and Institute of Medicine). 2007. *Rising above the gathering storm: Energizing and employing America for a brighter economic future.* Washington, DC: The National Academies Press. https://doi.org/10.17226/11463.

NAS, NAE, and IOM. 2009. *On being a scientist: A guide to responsible conduct in research*, 3rd edition. Washington, DC: The National Academies Press. https://doi.org/10.17226/12192.
NAS, NAE, and IOM. 2010. *Rising above the gathering storm, revisited: Rapidly approaching category 5*. Washington, DC: The National Academies Press. https://doi.org/10.17226/12999.
NASEM (National Academies of Sciences, Engineering, and Medicine). 2016a. *Gene drives on the horizon: Advancing science, navigating uncertainty, and aligning research with public values.* Washington, DC: The National Academies Press. https://doi.org/10.17226/23405.
NASEM. 2016b. *Genetically engineered crops: Experiences and prospects.* Washington, DC: The National Academies Press. https://doi.org/10.17226/23395.
NASEM. 2017a. *Preparing for future products of biotechnology*. Washington, DC: The National Academies Press. https://doi.org/10.17226/24605.
NASEM. 2017b. *Securing advanced manufacturing in the United States: The role of manufacturing USA: Proceedings of a workshop.* Washington, DC: The National Academies Press. https://doi.org/10.17226/24875.
NASEM. 2017c. *Software update as a mechanism for resilience and security: Proceedings of a workshop.* Washington, DC: The National Academies Press. https://doi.org/10.17226/24833.
NASEM. 2017d. *Undergraduate research experiences for STEM students: Successes, challenges, and opportunities.* Washington, DC: The National Academies Press. https://doi.org/10.17226/24622.
NASEM. 2018a. *Biodefense in the age of synthetic biology*. Washington, DC: The National Academies Press. https://doi.org/10.17226/24890.
NASEM. 2018b. *Graduate STEM education for the 21st century.* Washington, DC: The National Academies Press. https://doi.org/10.17226/25038.
NASEM. 2018c. *Indicators for monitoring undergraduate STEM education*. Washington, DC: The National Academies Press. https://doi.org/10.17226/24943.
NASEM. 2019. *Minority serving institutions: America's underutilized resource for strengthening the STEM workforce.* Washington, DC: The National Academies Press. https://doi.org/10.17226/25257.
NIH (National Institutes of Health). 2018. *Foreign influences on research integrity*. 117th Meeting of the Advisory Committee to the Director, December 13. https://acd.od.nih.gov/documents/presentations/12132018ForeignInfluences.pdf (accessed August 12, 2019).
Noyce, R. S., S. Lederman, and D. H. Evans. 2018. Construction of an infectious horsepox virus vaccine from chemically synthesized DNA fragment. *PLoS One* 13:e0188453.
NRC (National Research Council). 1996. *Understanding risk: Informing decisions in a democratic society*. Washington, DC: National Academy Press. https://doi.org/10.17226/5138.
NRC. 2001. *Opportunities in biotechnology for future Army applications.* Washington, DC: National Academy Press. https://doi.org/10.17226/10142.
NRC. 2004. *Capturing the full power of biomaterials for military medicine: Report of a workshop*. Washington, DC: The National Academies Press. https://doi.org/10.17226/11063.
NRC. 2012. *Research frontiers in bioinspired energy: Molecular-level learning from natural systems: Report of a workshop*. Washington, DC: The National Academies Press. https://doi.org/10.17226/13258.
NSB and NSF (National Science Board and National Science Foundation). 2018. *Science and engineering indicators 2018*. NSB-2018-1. Alexandria, VA: National Science Foundation. https://www.nsf.gov/statistics/indicators (accessed October 16, 2019).
Ochs, C., J. Geller, Y. Perl, and M. A. Musen. 2016. A unified software framework for deriving, visualizing, and exploring abstraction networks for ontologies. *Journal of Biomedical Informatics* 62:90–105. doi: 10.1016/j.jbi.2016.06.008.
Oliveira, A. L. 2019. Biotechnology, big data and artificial intelligence. *Biotechnology Journal* 14(8):1800613.
Peccoud, J., J. E. Gallegos, R. Murch, W. G. Buchholz, and S. Raman. 2018. Cyberbiosecurity: From naive trust to risk awareness. *Trends in Biotechnology* 36:4–7. doi: 10.1016/j.tibtech.2017.10.012.

Powell, P. 2008. Heparin's deadly side effects. *Time*, November 13. https://web.archive.org/web/20121216232624/http://www.time.com/time/magazine/article/0,9171,1858870-1,00.html (accessed July 5, 2019).

Reif, R. 2019. Letter to the MIT community: Immigration is a kind of oxygen. *MIT News Office*, June 25. http://news.mit.edu/2019/letter-community-immigration-is-oxygen-0625 (accessed July 3, 2019).

Richardson, L. C., N. D. Connell, S. M. Lewis, E. Pauwels, and R. S. Murch. 2019. Cyberbiosecurity: A call for cooperation in a new threat landscape. *Frontiers in Bioengineering and Biotechnology* 7:99. doi: 10.3389/fbioe.2019.00099.

Robinson, G. E., C. M. Grozinger, and C. W. Whitfield. 2005. Sociogenomics: Social life in molecular terms. *Nature Reviews Genetics* 6(4):257–270.

Ronquillo, J. G., J. E. Winterholler, K. Cwikla, R. Szymanski, and C. Levy. 2018. Health IT, hacking, and cybersecurity: National trends in data breaches of protected health information. *JAMIA Open* 1(1):15–19.

Saey, T. H. 2018. Genealogy databases could reveal the identity of most Americans. *Science News*, October 12. https://www.sciencenews.org/article/genealogy-databases-could-reveal-identity-most-americans (accessed October 16, 2019).

Shabani, M., and P. Borry. 2018. Rules for processing genetic data for research purposes in view of the new EU General Data Protection Regulation. *European Journal of Human Genetics* 26(2):149–156. doi: 10.1038/s41431-017-0045-7.

Shields, M. 2017. ChemChina clinches landmark $43 billion takeover of Syngenta. *Reuters*, May 5. https://www.reuters.com/article/us-syngenta-ag-m-a-chemchina/chemchina-clinches-landmark-43-billion-takeover-of-syngenta-idUSKBN1810CU (accessed September 5, 2019).

Smith, S., and J. Marchesini. 2007. *The craft of the system security*. Boston, MA: Person Education.

Stark, Z., L. Dolman, T. A. Manolio, B. Ozenberger, S. L. Hill, M. J. Caulfied, Y. Levy, D. Glazer, J. Wilson, M. Lawler, T. Boughtwood, J. Braithwaite, P. Goodhand, E. Birney, and K. N. North. 2019. Integrating genomics into healthcare: A global responsibility. *American Journal of Human Genetics* 104(1):13–20.

Taylor, D. O. Forthcoming. Patent eligibility and investment. SMU Dedman School of Law Legal Studies Research Paper No. 414. *Cardoza Law Review*. http://dx.doi.org/10.2139/ssrn.3340937 (accessed November 1, 2019).

Toga, A. W., and I. D. Dinov. 2015. Sharing big biomedical data. *Journal of Big Data* 2:7. doi: 10.1186/s40537-015-0016-1.

Tollefson, J. 2019. Chinese Americans uneasy as tensions disturb research. *Nature* 570:13.

Tucker, T. 2019. U.S. Army making synthetic biology a priority. *Government Executive*, July 1. https://www.govexec.com/defense/2019/07/us-army-making-synthetic-biology-priority/158145 (accessed July 3, 2019).

Tumpey, T. M., C. F. Basler, P. V. Aguilar, H. Zeng, A. Solórzano, D. E. Swayne, N. J. Cox, J. M. Katz, J. K. Taubenberger, P. Palese, and A. García-Sastre. 2005. Characterization of the reconstructed 1918 Spanish influenza pandemic virus. *Science* 310(5745):77–80.

U.S. Chamber of Commerce. 2017. *Made in China: Global ambitions built on local protections*. https://www.uschamber.com/sites/default/files/final_made_in_china_2025_report_full.pdf (accessed October 19, 2019).

U.S. Department of Commerce. 2018. Review of controls for certain emerging technologies. *Federal Register* 83(Nov. 19):58201–58202.

USGCRP (U.S. Global Change Research Program). 2018. *Impacts, risks, and adaptation in the United States: Fourth national climate assessment*, Vol. II. Washington, DC: U.S. Global Change Research Program. doi: 10.7930/NCA4.2018.

USPTO (U.S. Patent and Trademark Office). 2014. *2014 Interim guidance on patent subject matter eligibility. Federal Register* 79:74618–74633. https://www.govinfo.gov/content/pkg/FR-2014-12-16/pdf/2014-29414.pdf (accessed September 6, 2019).

USPTO. 2015. *July 2015 update: Subject matter eligibility*. Alexandria, VA: USPTO. https://www.uspto.gov/sites/default/files/documents/ieg-july-2015-update.pdf (accessed October 19, 2019).

USPTO. 2017. *Patent eligible subject matter: Report on views and recommendations from the public.* July. https://www.uspto.gov/sites/default/files/documents/101-Report_FINAL.pdf (accessed September 6, 2019).

USPTO. 2019a. *2019* Revised patent subject matter eligibility guidance. *Federal Register* 84(4):50–57. https://www.govinfo.gov/content/pkg/FR-2019-01-07/pdf/2018-28282.pdf (accessed September 6, 2019).

USPTO. 2019b. *October 2019 update: Subject matter eligibility (issued October 17, 2019).* https://www.uspto.gov/sites/default/files/documents/peg_oct_2019_update.pdf (accessed October 17, 2019).

USTR (U.S. Trade Representative). 2018a. *Findings of the investigation into China's acts, policies, and practices related to technology transfer, intellectual property, and innovation under Section 301 of the Trade Act of 1974*. Executive Office of the President. https://ustr.gov/sites/default/files/Section%20301%20FINAL.PDF (accessed March 12, 2020).

USTR. 2018b. *Update concerning China's acts, policies and practices related to technology transfer, intellectual property, and innovation*, November 20. Executive Office of the President. https://ustr.gov/sites/default/files/enforcement/301Investigations/301%20Report%20Update.pdf (accessed March 12, 2020).

USTR. 2019. *2018 Report to Congress on China's WTO compliance*. https://ustr.gov/sites/default/files/2018-USTR-Report-to-Congress-on-China%27s-WTO-Compliance.pdf (accessed September 5, 2019).

Van Noorden, R. 2013. White House announces new U.S. open-access policy. *Nature Newsblog*, February 22. http://blogs.nature.com/news/2013/02/us-white-house-announces-open-access-policy.html (accessed September 5, 2019).

Vest, C. M. 2013. *Testimony before the U.S. House of Representatives Committee on Science, Space and Technology, Subcommittee on Oversight, "Espionage Threats at Federal Laboratories: Balancing Scientific Cooperation while Protecting Critical Information,"* May 16. https://docs.house.gov/meetings/SY/SY21/20130516/100836/HHRG-113-SY21-Wstate-VestC-20130516.pdf (accessed March 12, 2020).

Vlassov, V. 2007. Russian clinical research is threatened by ban on export of samples. *British Medical Journal* 334(7606):1237. doi: 10.1136/bmj.39241.621863.DB.

Wee, S. 2019. China uses DNA to track its people, with the help of American expertise. *The New York Times*, February 21. https://www.nytimes.com/2019/02/21/business/china-xinjiang-uighur-dna-thermo-fisher.html (accessed October 16, 2019).

White House Office of the Press Secretary. 2013. *Presidential policy directive—critical infrastructure security and resilience.* https://obamawhitehouse.archives.gov/the-press-office/2013/02/12/presidential-policy-directive-critical-infrastructure-security-and-resil (accessed October 16, 2019).

Williams, P. A., and A. J. Woodward. 2015. Cybersecurity vulnerabilities in medical devices: A complex environment and multifaceted problem. *Medical Devices (Auckland, N.Z.)* 8:305–316. doi: 10.2147/MDER.S50048.

Zaveri, M. 2019. Wary of Chinese espionage, Houston cancer center chose to fire 3 scientists. *The New York Times*, April 22. https://www.nytimes.com/2019/04/22/health/md-anderson-chinese-scientists.html (accessed June 18, 2019).

Zhang, S. 2016. DNA got a kid kicked out of school—and it'll happen again. *Wired*, February 1. https://www.wired.com/2016/02/schools-kicked-boy-based-dna (accessed October 16, 2019).

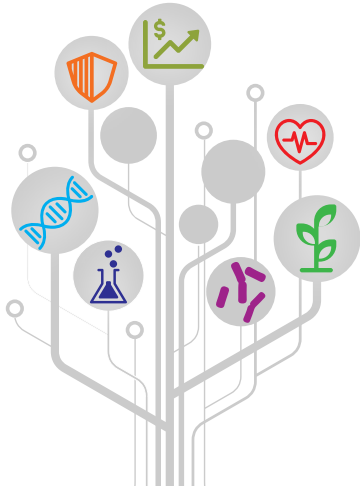
Zheng, S. 2019a. China issues official warning to students hoping to go to U.S. *South China Morning Post*, June 3. https://www.scmp.com/news/china/diplomacy/article/3012884/china-issues-official-warning-students-hoping-go-us (accessed July 3, 2019).

Zheng, S. 2019b. Chinese told to raise safety awareness in U.S. travel advisory. *South China Morning Post*, June 4. https://www.scmp.com/news/china/diplomacy/article/3013046/chinese-travellers-told-raise-safety-awareness-us-travel (accessed July 3, 2019).

PART IV

STRATEGIES FOR SAFEGUARDING THE U.S. BIOECONOMY

The final part of the report builds on the preceding three parts to synthesize and present the committee's overall conclusions and recommendations, for which context and the committee's rationale are provided. After examining the definition and landscape of the bioeconomy, evaluating metrics for its measurement, identifying methods for horizon scanning, and enumerating the associated economic and national security risks and policy gaps, the committee reached a number of overarching conclusions. These conclusions led the committee to provide recommendations targeted to the federal government, policy makers, and all bioeconomy stakeholders (i.e., all the individual researchers, institutions, companies, agencies, and relevant persons associated with the life sciences research enterprise).



8 OVERALL CONCLUSIONS AND RECOMMENDATIONS

The integration of engineering practices and principles, as well as advances in computing and information sciences, has transformed the life sciences and biotechnology, opening up new avenues for discovery, innovation, job creation, and economic growth while also raising a number of security issues. It is in this context that this committee was asked to analyze the current U.S. bioeconomy, consider how to define and measure it, and identify risks and policy gaps that need to be addressed to safeguard its continued advancement.

In the preceding chapters, the committee has examined the definition of the bioeconomy and the landscape covered by that definition. The committee also has reviewed and evaluated metrics used to determine the value of the bioeconomy and the leadership position of the U.S. bioeconomy in the context of the global bioeconomy. The committee has explored the ecosystem of the U.S. bioeconomy and methods for horizon scanning and foresight. Lastly, the committee has identified associated economic and national security risks and policy gaps. This chapter provides the committee's overall conclusions and recommendations, integrating at a higher level the various topics covered in the report, and offers a path for safeguarding the U.S. bioeconomy while sustaining innovation and growth.

DEFINING THE U.S. BIOECONOMY

The committee was asked to "outline the landscape of the U.S. bioeconomy," which required an examination of past descriptions of the bioeconomy (international and U.S.-based studies). Drawing on its members' own expertise, its information-gathering sessions, and its examination of past attempts to define the bioeconomy, the committee recognized immediately the breadth of activities and disciplines that are either rooted in or becoming integrated with the life sciences and biotechnology. Therefore, the committee drew the following conclusion:

Conclusion: The U.S. bioeconomy is a broad and diverse enterprise that spans many scientific disciplines and sectors and includes a wide and dynamic range of stakeholders.

In addition to exploring the landscape of disciplines and activities associated with the life sciences, the committee holistically examined the ecosystem that translates basic biological research into products and services. Basic life sciences research often begins with public investment in research and training of scientists working in academic and federal research settings or within the research and development (R&D) departments of corporations. In addition to these traditional stakeholders, many large research settings have spurred the development of local innovation ecosystems bringing in a wider range of stakeholders, such as citizen science laboratories, incubator spaces, start-up companies, small businesses, and partnerships with larger industrial companies. These innovation ecosystems have the potential to accelerate the translation of basic research or the realization of new concepts into practical applications for agriculture, human health, energy, and industrial manufacturing.

The generation, analysis, sharing, and application of large biological datasets have been associated with increased use of computational capacity and information sciences within the bioeconomy. These advances in informatics, together with the adoption of engineering principles in biological R&D and the current genome-editing revolution, are opening up new application areas for biotechnology and life sciences research. Collectively, these developments are expanding the reach of the bioeconomy into many varied sectors. A new definition is therefore needed to better capture the dynamism of the U.S. bioeconomy.

Recommendation 1: For purposes of demarcating the scope and reach of the U.S. bioeconomy and establishing a uniform framework for valuing the bioeconomy and its assets, the U.S. government should adopt the following definition of the U.S. bioeconomy:

The U.S. bioeconomy is economic activity that is driven by research and innovation in the life sciences and biotechnology, and that is enabled by technological advances in engineering and in computing and information sciences.

As discussed in more detail in Chapter 2, this definition recognizes the increasing contributions being made by other disciplines to advance biological research and encompasses the contributions made by biological discovery to sectors that in the past would not have been considered "biological." In Chapter 2, several examples illustrate the scope and reach of the bioeconomy. Recognizing that a definition of the U.S. bioeconomy needs to be flexible enough to allow for the future incorporation of new developments, the above definition does not limit the scope of the bioeconomy to particular sectors, technologies, or processes.

Having a definition that captures the breadth and depth of this dynamic enterprise provides a starting point for a common understanding of the boundaries of the bioeconomy and its transdisciplinary nature. Having a standard and consistent definition could also enable the U.S. government to better assess the current state of the bioeconomy, develop strategies for supporting and safeguarding its continued growth, devise metrics and data collection efforts to track its growth and conduct economic assessments, and allow policy makers to keep abreast of advances that have the potential to pose new national or economic security challenges.

MEASURING THE U.S. BIOECONOMY

The committee was also tasked to outline approaches for assessing the value of the bioeconomy and to identify intangible assets that may not be well captured by those approaches. The committee reviewed and summarized previous attempts to value the U.S. bioeconomy and discussed some of the drawbacks of those approaches. However, existing studies of the bioeconomy do not capture the activities encapsulated by the definition of the bioeconomy put forth in this report. To assess the value of the bioeconomy, the committee used the above definition to identify the primary segments (components or domains) of the bioeconomy and the data that would be needed to assess the bioeconomy's full value. Given the breadth and scope of the bioeconomy, identifying the data sources and components necessary to assess its value was an enormous effort, leading the committee to the following conclusion:

Conclusion: Measuring the bioeconomy is challenging since it has extended beyond the traditional biobased sectors of agriculture, biomedical science, and industrial biotechnology.

Adequately assessing the economic contribution of the bioeconomy to the larger U.S. economy could go a long way toward raising awareness of the importance of the U.S. bioeconomy and the need to monitor and safeguard it. A full assessment of the inputs and outputs of the bioeconomy could also enable future analysis of how investment in basic research is tied to productivity in this area, thus enabling better tracking of the outcomes of public investments. This enhanced tracking could serve as an indicator of the health of the sector, allow for an assessment of the impact of policy changes on the economic potential of the bioeconomy (or its subsectors), and help identify areas of growth that are worth protecting from a security standpoint.

In Chapter 3, the committee discusses various conceptual frameworks that could be used to determine the value of the bioeconomy and the merits and limitations of each. Moving beyond the three primary segments of the U.S. bioeconomy (agriculture, bioindustrial, and biomedical), the committee needed to determine the subset of these primary segments for which economic activity data are captured. Thus, the committee identified six segments within the broad category of goods and services, which includes materials, business services, and consumer products. At this level, the following six segments are taken as an approximation of the bioeconomy, as best as can be determined from the available data, and recognizing that they incompletely capture the bioeconomy as the committee has defined it: genetically engineered crops/products; biobased industrial materials (which include the agricultural feedstocks used for fermentation and other downstream processes); biopharmaceuticals and biologics and other pharmaceuticals; biotechnology consumer products; biotechnology R&D business services, including laboratory testing and purchased equipment services; and the design of biological data-driven patient health care solutions. Furthermore, the bioeconomy draws on specialized equipment and services, and produces intangible assets that all need to be considered and accounted for to determine the full value of the bioeconomy.

Following this economic categorization and to find data on the value added for each user-driven segment, the committee identified the relevant North American Industry Classification System (NAICS) codes, found estimates for how much of the activity included within a particular segment is related to the bioeconomy, and tabulated a sum of the value of each segment based on the available data (as summarized in Box 8-1). From this analysis, the committee determined that the U.S. bioeconomy represented roughly 5.1 percent of the gross domestic product (GDP) in 2016, or $959.2 billion (see Chapter 3 for a fuller discussion of this process). However, given that innovation can lead to the replacement of traditional products with biobased or bioeconomy-relevant products, it is possible

BOX 8-1
Framework for Valuing the Bioeconomy

1. Set boundaries for the definition of the bioeconomy to identify primary segments of interest (see Chapter 2).
2. Identify subsets of the primary segments to be included, encompassing relevant bioeconomy-specific equipment investments (e.g., sequencing machines) and services (e.g., biotechnology patent and legal services) and intangible assets produced and/or curated for use by the sector (e.g., genomic databases).
3. Identify the relevant production data that map to the delineated bioeconomy segments.
   a. Table 3-2 in Chapter 3 provides a mapping based on the North American Industry Classification System (NAICS) codes currently used by the U.S. Census Bureau to collect detailed data on the value of production.
      — Certain bioeconomy activities are inherently narrower than existing NAICS codes, and measuring those activities requires developing estimates based on auxiliary sources (or new NAICS codes), or building new aggregates from establishment-level survey or administrative microdata.
      — For each biobased production activity, determine the portion that is currently versus potentially (under existing technology) biobased (e.g., determine what percentage of plastics are made through a biobased process).
   b. Obtain estimates for value added for each relevant bioeconomy activity based on the same methods and data used in national accounts ("GDP by industry").
   c. Determine appropriate interindustry linkages and sources of supply (i.e., domestic versus foreign) and estimate relevant input-output "multipliers" based on these linkages.
4. The sum of value added estimates is the direct impact of bioeconomy production on the U.S. economy; the additional value added implied by input-output multipliers estimates the total contribution of the bioeconomy to the U.S. economy.

that this figure is an underestimation. And over the course of its analysis, the committee determined that significant data gaps were created by current classification and reporting mechanisms, which is sure to have an impact on the outcome of future valuations of the U.S. bioeconomy.

Conclusion: Existing data collection mechanisms for measuring economic activity are insufficient to monitor the bioeconomy holistically. Improved data collection is needed to better (1) understand the scope and reach of the U.S. bioeconomy, (2) provide a comprehensive valuation of the U.S. bioeconomy, (3) support U.S. decision

making with regard to the bioeconomy, and (4) identify indicators of leadership and global connections.

Recommendation 2: The U.S. Department of Commerce and the U.S. National Science Board should expand and enhance data collection efforts relevant to the economic contribution of the U.S. bioeconomy as defined by this committee.

The committee developed a subset of recommendations that would be most likely to expand and enhance data collection efforts to facilitate future valuations of the bioeconomy.

Recommendation 2-1: The U.S. Department of Commerce and other relevant agencies and entities involved in the collection of U.S. economic data should expand their collection and analysis of bioeconomic data. The U.S. Department of Commerce should obtain input from partners in science agencies and from nongovernmental bioeconomy stakeholders to supplement and guide these efforts.

These expanded data collection efforts could provide a foundation of information that could be used to inform other activities within the U.S. Department of Commerce related to the bioeconomy. In Chapter 3, the committee mentions a number of other actions or activities that the U.S. Department of Commerce currently oversees that could benefit from an expanded collection and analysis of the activities of the bioeconomy and the permeation of products, processes, and services. The following two recommendations relate specifically to two of those activities.

Recommendation 2-2: The existing North American Industry Classification System (NAICS) and North American Product Classification System (NAPCS) codes should be revised to more accurately capture and track commercial activity and investments related to the biological sciences and track the growth of individual segments of the bioeconomy (e.g., biological production of chemicals and materials). In addition, the U.S. Department of Commerce's Office of Technology Evaluation should undertake a study aimed at richer characterization of the permeation of biologically based products, processes, and services in the U.S. economy. Such a study would greatly inform revisions of the NAICS and NAPCS codes. Additionally, the U.S. Census Bureau should refine and regularly collect comprehensive statistics on bioeconomic activities.

Currently, there are some codes that are wholly included within this study's definition of the bioeconomy, such as Research and Development in Biotechnology (NAICS 541714) and Biomass Electric Power Generation (NAICS 221117). However, other components, such as soy ink production, are currently lost in the broader categories that would appear not to be part of the bioeconomy, such as Printing Ink Manufacturing (NAICS 325910). Additionally, some components of the U.S. bioeconomy, such as synthetic biology, are worth tracking because of the apparent growth and sense of expansion within the scientific community, but are not currently captured in any single code or set of codes to enable an accurate economic assessment. Given the importance of this classification system for tracking the economic data associated with various activities, one can imagine the usefulness of codes that would specifically track developments in synthetic biology, such as Synthetic Biology R&D Services, Consumer Biotech, Synthetic Biology Devices, and Biotechnology Automation.

The NAICS and NAPCS codes are updated every 5 years through a process that involves soliciting and reviewing proposals from the public.[1] In addition to this normal process, the committee suggests that a detailed study focused on examining the pervasiveness of bioeconomy products, processes, and services could be instrumental in informing future revisions. The U.S. Department of Commerce's Office of Technology Evaluation analyzes "critical technologies and industrial capabilities of key defense-related sectors,"[2] using, among other techniques, industry-specific surveys to which recipients are required by law to respond.[3] The committee believes that the bioeconomy is sufficiently important to national defense to warrant the use of this capability and that the outcome should be used to inform future revisions of the NAICS and NAPCS codes.

Recommendation 2-3: The Bureau of Economic Analysis of the U.S. Department of Commerce should lead the development of bioeconomy satellite accounts linked to central national accounts. These satellite accounts should include databases of biological information

[1]For more information, see https://www.census.gov/eos/www/naics/reference_files_tools/NAICS_Update_Process_Fact_Sheet.pdf.

[2]See the "Industrial Base Assessment" page on the website of the U.S. Department of Commerce, Bureau of Industry and Security at https://www.bis.doc.gov/index.php/other-areas/office-of-technology-evaluation-ote/industrial-base-assessments.

[3]The U.S. Department of Commerce's Office of Technology Evaluation exercises authorities delegated by the President to the Secretary of Commerce under the Defense Production Act to obtain information that may be "necessary or appropriate" to enforce or administer that Act. For more information see, 50 U.S.C. § 4555(a), Section 705(a) of the Defense Production Act of 1950 (P.L. 81-774), as amended; Executive Order 13603.

as assets and over time be expanded to include environmental and health benefits attributable to the bioeconomy.

As described in Chapter 3, a satellite account is a system of economic data that portrays expenditures, production, and income generated by a specified set of activities. The creation and use of a bioeconomy satellite account could provide a flexible tracking mechanism that would be customizable and flexible across sectors. The committee sees great potential in such a tool for enabling better tracking of the growth and dynamism of the U.S. bioeconomy, particularly given that it could be used to explore new data collection and reporting methods and develop new accounting procedures that, once accepted, could become part of standard national income accounting procedures.

Recommendation 2-4: The U.S. National Science Board should direct the U.S. National Science Foundation to undertake new data collection efforts and analyses of innovation in the bioeconomy for the *Science and Engineering Indicators* report so as to better characterize and capture the depth and breadth of the bioeconomy, with an emphasis on identifying indicators that provide insight into U.S. leadership and competitiveness.

The *Science and Engineering Indicators* (*S&E*) report served as a valuable tool in the committee's analysis of the bioeconomy and its effort to understand leadership metrics. As noted in Chapter 4, however, the committee encountered many data gaps during its assessment, particularly around new trends and fields within the life sciences. Much of this has to do with the categorization and classification of particular activities. For example, it is not always clear whether such fields as biomedical engineering are classified within "engineering" or within "life sciences." These limitations are not different in concept from the limitations encountered when the committee was considering the NAICS codes. While the committee understands that changing the nature of the metrics and classification system can make historical comparisons very difficult, an effort is needed to enable capturing the dynamism of newly emerging fields. As many research disciplines continue to change and converge with other disciplines, it will be important for the *S&E* report to adjust its own data collections to capture these changes so it can continue to serve as a useful tool for tracking and understanding the state of the bioeconomy (and beyond).

SAFEGUARDING THE U.S. BIOECONOMY

Establishing a Coordinating Body

During the course of this study, the committee consistently heard that an "all of government" or "all of society" effort is needed to address some of the challenges facing the U.S. bioeconomy, particularly with respect to potential national or economic security concerns. While the committee recognizes that all of the stakeholders within the bioeconomy have a role to play, leadership and strategic direction are needed. Given the breadth of the bioeconomy across the many sectors discussed throughout this report, it is not surprising that life sciences research is distributed across many agencies and departments of the U.S. government (as explored in Chapter 5). This disaggregated distribution poses a significant challenge for large-scale coordination, particularly when there is no clear candidate agency to take leadership. Each agency and department has its defined mission space and associated scientific domain; therefore, no government agency has the mandate to monitor and assess the U.S. bioeconomy holistically, let alone determine a strategy for promoting and protecting it.

Conclusion: Given the lack of an obvious lead government agency for the bioeconomy, the committee concluded that a mechanism through which the science, economic, and security agencies could bridge the gaps in communication and coordination is needed.

Recommendation 3: The Executive Office of the President should establish a government-wide strategic coordinating body tasked with safeguarding and realizing the potential of the U.S. bioeconomy. To be successful, this coordinating body should be presided over by senior White House leadership, with representation from science, economic, regulatory, and security agencies. It should be responsible for relevant foresight activities and informed by input from a diverse range of relevant external stakeholders.

Having a coordinating body would overcome the concern that no single agency has the responsibility to monitor the bioeconomy holistically. Given the increase in specialized knowledge and the disciplinary convergence in the bioeconomy, it will be difficult for individual agencies, despite their ability to support their individual mission space, to identify policies, funding priorities, and areas of opportunity that would collectively strengthen the U.S. bioeconomy. Therefore, a U.S. government coordinating body informed by nongovernmental bioeconomy stakeholders is needed to create and implement a national strategy that will sustain and grow the bioeconomy. In addition, the inclusion of a specialized security

component could enable the development of policies that would strike the right balance between protecting the U.S. bioeconomy and mitigating the potential for negative impacts. It will be crucial for these discussions to involve not only scientific and security agencies but also economic agencies tasked with tracking indicators of the bioeconomy's growth and health.

Without stipulating how the U.S. government could organize such a coordinating body, the committee notes that precedents exist. Cross-governmental coordination can be accomplished through an interagency working group chartered independently or under one of the White House policy-making offices (e.g., the Office of Science and Technology Policy, the National Security Council, the National Science and Technology Council, the National Economic Council). Alternatively, the coordinating body could be established through a congressional mandate, as was the National Nanotechnology Initiative, a mechanism by which the U.S. government coordinates the R&D activities of 20 departments and agencies involved in nanotechnology.[4]

Over the course of its information-gathering sessions, the committee learned during its third such session in May 2019 that some coordinating activity was being actively discussed and in the early planning stages within the Executive Office of the President (EOP). In September 2019, the EOP released a request for information to gather stakeholder input,[5] which was followed by the White House Summit on America's Bioeconomy in October 2019 (EOP, 2019). However, these events did not describe or elaborate the structure, strategy, or membership of the agencies involved in this effort.

Furthermore, the committee identified the importance of engaging with nongovernmental stakeholders to inform this process. Examples of potential engagement strategies include the establishment of formal federal advisory committees, regular public convening activities, targeted outreach to different scientific communities and societies, and the use of public–private partnership agreements. Enabling the participation of industrial and academic leaders will facilitate the development of a strategy and supporting policies that address the needs of the bioeconomy.

---

[4]Originally proposed by the Clinton administration in 2000, the National Nanotechnology Initiative (NNI) was formally created in 2003 with passage of the 21st Century Nanotechnology Research and Development Act, P.L. 108-153. The Nanoscale Science, Engineering, and Technology Subcommittee of the National Science and Technology Council's Committee on Technology coordinates the NNI's planning, budgeting, program implementation, and review. Technical and administrative support and public outreach are provided by the National Nanotechnology Coordination Office. See "About the NNI" at www.nano.gov/about-nni.

[5]See https://www.federalregister.gov/documents/2019/09/10/2019-19470/request-for-information-on-the-bioeconomy.

Sustaining and Growing the U.S. Bioeconomy

In addition to recommending a coordinating body across the federal government and with nongovernmental stakeholders, the committee developed a subset of more specific recommendations designed to help sustain and grow the U.S. bioeconomy.

Recommendation 3-1: The coordinating body should develop, adopt, and then regularly update a living strategy with goals for sustaining and growing the U.S. bioeconomy. This strategy should be informed by an ongoing, formal horizon-scanning process within each of the relevant science agencies, as well as by input from industry, nongovernmental organizations, and academia. Additionally, through this strategy, the coordinating body should identify and raise awareness of means through which the U.S. government can advance the bioeconomy, including such existing means as government procurement of biobased products.

Setting a unified strategy for the bioeconomy informed by relevant governmental and nongovernmental bioeconomy stakeholders will enable meaningful coordination and alignment of individual agency efforts toward pursuing a common goal: sustaining, growing, and safeguarding the U.S. bioeconomy. Elements of such a strategy could include the support of innovative, multidisciplinary, and convergent research to drive biological discovery; maintenance of a robust talent base that is well prepared to join the bioeconomy workforce; prioritization of the development and maintenance of a modern, secure, and connected research infrastructure that best serves the needs of all bioeconomy stakeholders; and mechanisms for safeguarding the bioeconomy and its assets.

While creating a U.S. bioeconomy strategy would provide a powerful policy tool for relevant federal agencies, the committee emphasizes the importance of continually tracking developments in the bioeconomy and proactively incorporating these developments into the strategic and policy apparatus. Therefore, the committee stresses the importance of establishing an ongoing horizon-scanning and foresight process that will identify emerging developments in science and technology that could raise new issues or require new policy. A U.S. bioeconomy strategy linked to a horizon-scanning process would allow for an anticipatory approach that would permit the identification of new issues or the prioritization of those issues likely to have the greatest scientific, economic, and policy impact. Currently, policy makers cannot keep up with the rapid pace of developments in science and technology, and thus policy tends to be reactionary, and sometimes significantly delayed. As discussed in Chapter

7, policy and regulatory uncertainty also has the potential to dampen innovation.

Best practices for conducting a robust horizon-scanning process are enumerated in Chapter 6. In short, the committee suggests that each bioeconomy-relevant science agency establish a horizon-scanning process focused on identifying new issues, topics, and technology developments in its specific domain. As concluded in Chapter 6, there are four key considerations for establishing a horizon-scanning process: approach, scope, process, and timeframe (see Box 8-2). These agencies would report out to the larger government-wide coordinating body called for in Recommendation 3 every 2 years, thereby enabling a comprehensive scan across the full scope of the bioeconomy. Having these activities start within each of the relevant science agencies would ensure that there would be subject-matter experts involved in conducting the scan; however, unless an effort were undertaken to bring in nontechnical experts, these activities could be limited (as described in Chapter 6). The ultimate goal of these actions would be to (1) identify new technologies, markets, and data sources that could provide insights into the bioeconomy (from a policy, security, or economic assessment perspective); (2) identify specific and timely opportunities for the bioeconomy; and (3) identify disruptive events or other

BOX 8-2
Key Considerations in Horizon Scanning and Foresight for the Bioeconomy

1. Approach: The goal would be to design a horizon-scanning activity that is capable of feeding information into both scenario-planning and issue identification processes.
2. Scope: There are two levels at which the scope of the bioeconomy should be considered:
   a. Defining the bioeconomy—Given that the bioeconomy is broad and is increasingly penetrating new technical fields and economic sectors, a broad horizon-scanning effort will be needed to continuously monitor its scope.
   b. Tracking specific lines of development or policy issues—A detailed consultation process (such as the Delphi method) could be used to drill down into specific topics or to address specific questions.
3. Process: In the near term, horizon-scanning activities are likely to be human-driven; however, tools for automated data gathering are advancing and could be used to feed into a meta-review.
4. Timeframe: Combining horizon-scanning and foresight approaches will enable the identification of both near-term developments (foresight) and longer-term developments (horizon scanning).

threats. Lastly, given that establishment of the coordinating body the committee is recommending calls for the inclusion of the economic agencies, it is the committee's intention that the horizon-scanning activities described here would be linked to efforts to improve the data sources and economic metrics discussed in Recommendation 2 and explored more thoroughly in Chapters 3 and 4.

The last component of Recommendation 3-1 calls on the federal government to take stock of the actions that can be taken now to help grow and sustain the U.S. bioeconomy. Chief among those actions could be to use the power of federal procurement to drive the bioeconomy through the strategic procurement of biobased goods. As an example, strategic biobased procurement by government and industry procurement offices of the U.S. Department of Agriculture's BioPreferred Program would catalyze the creation of new markets and jobs. This program is designed to increase the development, use, and purchase of biobased products that are derived from agricultural, marine, and forestry materials. Although the Farm Bill mandates that federal agencies and contractors purchase biobased products when doing so does not impose cost or performance penalties, no regular report is available through which to understand the progress or scale of biobased procurement. Updating the reporting mechanisms involved in the federal procurement of biobased products, setting procurement targets, and increasing funding for the program to enable increased awareness and standardized reporting—such as a real-time public-facing dashboard to report federal progress in biobased procurement—would go a long way toward stimulating the bioeconomy and supporting jobs in rural areas where many source materials are concentrated. Encouraging private-sector retailers to feature BioPreferred products among their offerings would advance these goals even further.

Addressing the Economic and National Security Risks Pertaining to the Bioeconomy

This committee was tasked to "outline potential economic and national security risks and identify policy gaps pertaining to the collection, aggregation, analysis, and sharing of data and other outputs of the bioeconomy," as well as to examine whether particular features of the bioeconomy would require different protection mechanisms. In Chapter 7, the committee presents some identified risks and their potential implications. Where possible, the committee also discusses the relevant policy tools that could be used to address the identified risks. It should be noted that the committee performed this analysis solely on the basis of publicly available information.

The committee identified (1) risks that would harm the bioeconomy's continued growth or hamper the innovative ecosystem within which it currently operates, (2) risks from the theft of or asymmetries in access to intellectual property or key bioeconomy information that would confer a competitive advantage on another party at the expense of the U.S. bioeconomy, and (3) risks from misuse or hijacking of bioeconomy outputs or entities. To address these risks, the committee focused its recommendations on talent, foreign investment in U.S. research, and cybersecurity approaches.

Conclusion: Protecting the U.S. bioeconomy while preserving the open, collaborative environment required to sustain the bioeconomy will require a carefully considered balance.

The U.S. bioeconomy has historically benefited from participation in an open, global, and collaborative scientific environment that relies on the academic integrity of individuals and their willingness to adhere to research norms and values (IAP, 2016; NAS et al., 2009; NASEM, 2018). However, there has been increasing concern among some federal officials that the openness of the U.S. scientific enterprise puts its integrity and competitiveness at risk. Safeguarding the U.S. bioeconomy while protecting innovation and growth could be facilitated by developing a more thorough understanding of the mechanisms by which the open conduct of and participation in fundamental scientific research drive proprietary innovation by entrepreneurs, both within the United States and among economic competitors, and conversely, of how restrictions on openness may affect the scientific research environment. The tension between these two goals will require that policy makers strive for a balance that maximizes the benefits of scientific openness while protecting U.S. economic and security interests from countries that would exploit this nation's openness unfairly.

Funding and Sustaining the Bioeconomy Research Enterprise

Conclusion: The U.S. bioeconomy relies on a robust and well-funded research enterprise that seeds innovation and supports a technically skilled and diverse workforce.

Chapters 3, 4, and 5 explore the foundational role played by public investments in science and engineering research in driving America's research enterprise, investments that have built the university research and education system that continually produces more doctoral graduates than does any other country. These investments directly benefit the

U.S. bioeconomy given that growing fields, such as synthetic biology, will require a consistent influx of new minds to continue to drive innovation and discovery. Through partnerships between industry and high schools, community colleges, and universities, innovation ecosystems are creating opportunities for training and developing a talent pool to power the bioeconomy. These partnerships are expanding the potential workforce beyond Ph.D.-level researchers. However, as other countries scale up investments in their own life sciences research enterprises and begin to increase their scientific output, concerns arise about the ability of the United States to maintain its leadership. Currently, the United States remains among the world's leaders in public investment in the biological sciences, but erosion in support for government investment is a concern. Therefore, the committee makes the following recommendation:

Recommendation 4: To maintain U.S. competitiveness and leadership within the global bioeconomy, the U.S. government should prioritize investment in basic biological science, engineering, and computing and information sciences. In addition, talent development, at all levels, to support these research areas should be a high priority for future public investment.

Lack of coordinated funding across the science and engineering disciplines in support of a U.S. bioeconomy strategy has the potential to weaken the ecosystem that has enabled the translation of research and knowledge into innovative goods and services. The committee's analysis of past and current investments suggests that the rate of federal investment has become stagnant. Securing future U.S. leadership in the bioeconomy will likely require returning to investment levels characteristic of the 1990s and early 2000s. The present stagnation in federal investment is in contrast with the increasing investments of other countries. The number of countries that are creating and implementing their own bioeconomy strategies, often with considerable funding and resources to support these initiatives, is challenging continued U.S. leadership.

Insufficient federal funding for U.S. universities and bioeconomy training programs has the potential to diminish the ability to produce and retain a skilled technical workforce. Increased federal support for science, technology, engineering, and mathematics (STEM) education and partnerships between community colleges and industry aimed at growing a technically skilled workforce could create employment opportunities in U.S. regions whose traditional employment opportunities may have changed. As articulated in Chapter 5, for example, the development of biotechnology capabilities in rural areas holds promise, and investments in training

programs and facilities in these areas could open up new opportunities for those communities while growing the bioeconomy.

In addition to the importance of training a domestic bioeconomy workforce, the United States has historically benefited from the ability to attract students and scientists from around the world to its universities. International students constitute a significant fraction of the enrollments at U.S. colleges and universities, particularly in STEM disciplines at the graduate level, and foreign-born employees form a substantial component of the U.S. STEM workforce. These researchers have contributed immensely to the vibrant research enterprise that the United States currently enjoys. As explored in Chapter 7, however, a number of domestic and international factors could potentially complicate the nation's ability to attract and retain international scientists and engineers. As other countries increasingly prioritize their bioeconomies and create appealing locations for companies to establish their operations, opportunities for students and researchers to remain in their home countries will increase. Domestically, changes in visa policy and investigations into researchers with ties to foreign governments, talent programs, and funding also have the potential to discourage talented researchers from around the world from coming to the United States or even collaborating with U.S.-based scientists. For this reason, the committee makes the following recommendation:

Recommendation 4-1: The U.S. government should continue to support policies that attract and retain scientists from around the world who can contribute to the U.S. bioeconomy, recognizing that open academic engagement has been strongly beneficial to the U.S. scientific and technological enterprise, even as it inherently offers potential benefits to other countries as well. Policies intended to mitigate any economic and security risks posed by foreign researchers in U.S. research institutions should be formulated by U.S. security, science, and mission agencies working closely together, and through ongoing engagement with a group of recognized scientific leaders. Having this group able to be fully briefed on the threat environment will greatly facilitate these discussions, since access to classified, proprietary, or other nonpublic information may be needed.

Such discussions, if necessary, can be accomplished through a number of existing mechanisms in which scientific and industry leaders can provide advice on a classified basis. Examples include the National Science Advisory Board for Biosecurity or other federal advisory committee, or tasking of such groups as the JASONs or the President's Council of Advisors on Science and Technology to conduct an initial focused study

on the subject.[6] These discussions and/or studies could serve a number of purposes. They would permit scientific experts and federal officials to have a full and frank discussion of the rationale for proposed security policies. Policy makers would receive input on the direct and indirect consequences of potential security policies from those with first-hand experience conducting and/or administering state-of-the-art scientific research or technological entrepreneurship. Furthermore, members of the broader scientific community who were not in a position to participate in these discussions could have some confidence that colleagues with a deep understanding of how the scientific enterprise works were being consulted. Both scientists and policy makers should thereby have some assurance that experts from both communities were able to evaluate the evidence underlying proposed security policies and to have an informed discussion of the potential consequences of those policies.

Securing Value Chains and Examining Foreign Investments

Conclusion: Securing value chains vital to the U.S. bioeconomy will be necessary for its continued growth.

The committee recognizes that the U.S. bioeconomy needs to be able to sustain itself through securing of the value chains that fuel it. The continued development of biological routes to the production of previously non-biobased products will disrupt existing value chains as the bioeconomy continues to permeate into new sectors. The nation would face potential risks should critical parts of bioeconomy value chains be disrupted, such as through supply shortages, interruptions in transport, or reliance on single sources. The latter is particularly important if the single source is based overseas and thus subject to foreign export regimes, changes in political relationships, or other factors beyond U.S. control. Key components of bioeconomy value chains, key capabilities and sources of supply that are intrinsic to the U.S. bioeconomy and warrant being maintained entirely domestically, and mechanisms by which these capabilities and sources can be secured remain to be identified.

Conclusion: Bioeconomy subject-matter expertise is needed for examining transactions involving foreign investors.

As pointed out in Chapter 5, the transitional space where research is too applied for university-level development and yet still too risky

[6]The National Science Foundation has already announced a study by the JASONs to inform potential policy changes related to such concerns.

to justify industry investment in commercial application represents an opportunity for venture capital to help start-up companies thrive. However, the source of venture capital funding for these early- to mid-stage developers may require more scrutiny, particularly given the increasing trend toward foreign investment in U.S. bioeconomy companies and start-ups. In Chapter 7, the committee cites a few examples in which investments by nondomestic parties, either private capital- or state-backed, in U.S. bioeconomy businesses—both large, highly successful companies and smaller companies and start-ups—were undertaken with the goal of acquiring intellectual property.

The Committee on Foreign Investment in the United States[7] (CFIUS) is responsible for reviewing potential foreign investments in and purchases of U.S. companies. In August 2018, the Foreign Investment Risk Review Modernization Act was signed into law, expanding CFIUS's purview. Given the specialized nature of the bioeconomy, the committee determined that CFIUS will likely require subject-matter expertise to adequately assess the implications of particular investments in U.S. bioeconomy entities.

Recommendation 5: The U.S. government should convene representatives from its science and economic agencies who can access relevant classified information to provide security agencies with subject-matter expertise so as to (1) identify aspects of bioeconomy global value chains that are vital to U.S. interests and to which access must be ensured, and (2) assist the Committee on Foreign Investment in the United States in assessing the national security implications of foreign transactions involving the U.S. bioeconomy.

Prioritizing Cybersecurity and Information Sharing

Conclusion: The digitization of biology and biotechnology automation are key drivers that enable the bioeconomy. Inadequate cybersecurity practices and protections expose the bioeconomy to significant new risks.

Life sciences research is driven by the collection and analysis of large amounts of data that are often generated through the use of automated and network-connected instruments. The ability to process such data is increasingly enabled by high-throughput laboratory technologies, computational processing power, and information exchange and storage capacity.

[7]See https://home.treasury.gov/policy-issues/international/the-committee-on-foreign-investment-in-the-united-states-cfius.

Related trends—such as the use of machine learning to identify patterns, the integration of information across diverse life sciences datasets, and the easy storage and sharing of data—increasingly underpin innovation in pharmaceutical and agricultural product development, personalized medicine, disease surveillance, improved design of genetic circuits and biosynthetic pathways in synthetic biology, large-scale ecosystem studies, biomanufacturing, and many other areas.

Recommendation 6: All bioeconomy stakeholders should adopt best practices for securing information systems (including those storing information, intellectual property, private-proprietary information, and public and private databases) from digital intrusion, exfiltration, or manipulation.

While large companies tend to be aware of traditional cyber concerns and have information technology infrastructures that provide protection, smaller companies and academic institutions may not always be aware that they, too, are targets for cyber intrusions. Therefore, the committee recommends that all stakeholders (companies of all sizes, academic institutions, government agencies, and others) adopt best practices to create an organizational culture that promotes and values cybersecurity. Adoption of these best practices could be accomplished in a number of different ways, such as with training for all researchers within the bioeconomy to increase awareness of cybersecurity threats and vulnerabilities; adoption of the National Institute of Standards and Technology's Cybersecurity Framework (which can be adapted for a wide range of organization sizes and types); and for some organizations, the appointment of chief information security officers.

Recommendation 7: To protect the value and utility of databases of biological information, U.S. science funding agencies should invest in the modernization, curation, and integrity of such databases.

Biological datasets increasingly underpin many of the advances driving the U.S. bioeconomy. Researchers receiving federal funding are often mandated to share their data and make them publicly available, thereby growing these vital databases rapidly. As explored in Chapter 5, however, the potential for redundancy, inaccuracy, and even conflicting entries poses a significant problem that is growing with the continued deluge of data. Attempts to merge, curate, and validate databases and redundant entries have demonstrated the considerable effort required; however, the potential net benefit for research would be immense. While the committee recognizes that the science-funding agencies are facing ever smaller

budgets, the investments (in time and resources) made to acquire data create a sufficiently compelling reason to increase investment in maintaining databases. It is difficult to imagine all the potential downstream applications of life sciences data; therefore, rather than require repetitive efforts to recreate datasets, the committee recommends increasing investment in databases. While some may consider the trade-off too great between funding new research and funding the modernization, curation, and integrity of databases, the committee believes this view is myopic. This report articulates the importance of large databases of biological information for fueling innovation and driving the bioeconomy, given that they are a source of novel discoveries while also enabling the improvement of machine learning and other computational tools. In Recommendation 4, the committee articulates the importance of increasing funding in the life sciences and related disciplines, and this recommendation further underscores the need for additional funding that is more focused on this important component of the bioeconomy.

Recommendation 8: Bioeconomy stakeholders should pursue membership in one or more relevant Information Sharing and Analysis Centers or Information Sharing and Analysis Organizations, or consider creating a new sector-based information sharing organization for members of the bioeconomy. The Cybersecurity and Infrastructure Security Agency within the U.S. Department of Homeland Security should convene bioeconomy stakeholders to build awareness about relevant models for sharing information on cyberthreats. Those convened should consider whether an active repository is needed to host and maintain key bioeconomy-related open-source software, algorithm components, and datasets.

The bioeconomy relies on the use of open-source software, which means the software and its source code are openly available to anyone. However, the software industry has learned that simply making code open-source does little or nothing to guarantee its quality, robustness, and security. Within the bioeconomy, several major open-source programs are used by a significant number of companies, universities, and national laboratories. In addition, many researchers develop highly individualized, bespoke software for use in a particular research effort or application that they then make available to others. In some cases, open-source software is available only for download, and any subsequent modification would be done by individual researchers to meet their specific needs. In other cases, however, source code used within the bioeconomy can be readily modified by anyone who wishes to do so. This introduces the potential for misuse, for example, if a malicious actor were to purposefully introduce a

vulnerability into source code that enabled unauthorized access by third parties. These concerns could potentially be mitigated by establishing a more formal repository of open-source software for the bioeconomy, a formal regime for controlling changes to source code, a testing regimen for any changes to the code, and restrictions on who can make changes. Programs and incentives could be established to improve relevant software. Bioeconomy stakeholders would need to determine what type of entity is most appropriate to manage such a regime. Although no entity currently performs this role for this sector, an information-sharing and analysis group, or perhaps a special-purpose consortium, could potentially serve as such an entity.

Participation in an information-sharing group could additionally enable bioeconomy stakeholders to share experiences in detecting, mitigating, and preventing cyber intrusions, as has been done in many infrastructure sectors. Cyberthreat actors may pursue campaigns against one company or against an entire sector. When an entire sector is targeted, information-sharing activities across the sector could be effective in mitigating the impact of such a campaign by enabling rapid communication and sharing of patches or strategies to counter an attack.

OPPORTUNITIES FOR INTERNATIONAL ENGAGEMENT

Finally, the committee recognizes that the U.S. bioeconomy exists in the broader context of a global bioeconomy. Science is an increasingly global enterprise, and as discussed throughout this report, there is immense value to be gained from participating in a scientific enterprise that enables and embraces the free flow of ideas and discussion, the wide dissemination of published results, and collaboration across disciplines and borders. The benefits of such a system are available to all participants. Moreover, future challenges will be global in nature and require a coordinated, global response. This will entail partnering with others who are actively growing and investing in their own bioeconomies, especially those who are likewise committed to open science, open economic development, and responsible research and innovation. It is essential that the United States continue its role in international collaborations and play an active role in the global bioeconomy.

Of course, one must recognize that not everything can and should be shared and that some actors within the system seek to take advantage of the current state of openness. It is for these reasons that policies, guidelines, and reporting mechanisms related to responsible science and ethical conduct have been devised to prevent abuses of the system. Chapter 7 explores concerns about uneven trade practices, the lack of reciprocity with respect to sample- and data-sharing practices, and even regulatory

regimes that make it more difficult for companies to bring their products to nondomestic markets. These practices, and others like them, have the potential to hinder the progress of research, the spread of innovative methods and ideas, and realization of the social and economic benefits of new products. These practices could also undermine the trust among collaborations and potentially lead to overreactive policies and decisions that could hinder the U.S. bioeconomy (these ideas and potential consequences are discussed more thoroughly in Chapter 7). Therefore, with a view toward striking a balance between security and engagement, the committee makes the following recommendation:

Recommendation 9: Through such entities as the World Trade Organization and the Organisation for Economic Co-operation and Development, as well as through other bilateral and multilateral engagements, the U.S. government should work with other countries that are part of the global bioeconomy to foster communication and collaboration. The goals of such international cooperation would be to (1) drive economic growth, (2) reinforce governance mechanisms within a framework that respects international law and national sovereignty and security, and (3) create a level playing field.

U.S. agencies tasked with international engagement and agreements could play a central role in facilitating discussions among countries to increase the benefits of an open research enterprise for all and incentivizing all to adhere to the agreed-upon norms.

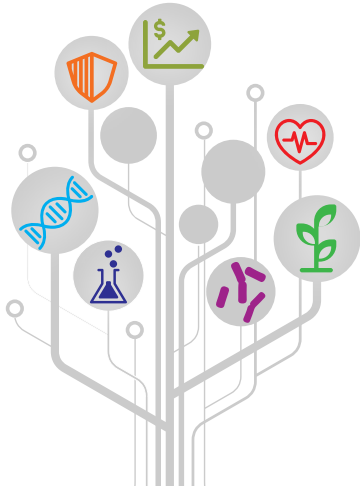
REFERENCES

EOP (Executive Office of the President). 2019. *Summary of the White House summit on America's bioeconomy.* Washington, DC. https://www.whitehouse.gov/wp-content/uploads/2019/10/Summary-of-White-House-Summit-on-Americas-Bioeconomy-October-2019.pdf (accessed October 22, 2019).

IAP (InterAcademy Partnership). 2016. *Doing global science: A guide to responsible conduct in the global research enterprise.* https://www.interacademies.org/33345/Doing-Global-Science-A-Guide-to-Responsible-Conduct-in-the-Global-Research-Enterprise (accessed September 6, 2019).

NAS, NAE, and IOM (National Academy of Sciences, National Academy of Engineering, and Institute of Medicine). 2009. *On being a scientist: A guide to responsible conduct in research, 3rd edition*. Washington, DC: The National Academies Press. https://doi.org/10.17226/12192.

NASEM (National Academies of Sciences, Engineering, and Medicine). 2018. *Open science by design: Realizing a vision for 21st century research*. Washington, DC: The National Academies Press. https://doi.org/10.17226/25116.



A
COMMITTEE BIOGRAPHIES

Dr. Thomas M. Connelly, Jr. (NAE), *Chair*, is the executive director and the chief executive officer of the American Chemical Society. He also currently serves as the chair of the National Academies of Sciences, Engineering, and Medicine's Division on Earth and Life Studies. Dr. Connelly retired in December 2014 from DuPont, where he was the executive vice president, the chief innovation officer, and a member of the company's Office of the Chief Executive. At DuPont, he was responsible for science and technology and geographic regions outside the United States, as well as integrated operations, which include operations, sourcing and logistics, and engineering. Also at DuPont, he led businesses and research and development organizations while based in the United States, Europe, and Asia. Dr. Connelly graduated with highest honors from Princeton University with degrees in chemical engineering and economics. As a Winston Churchill Scholar, he received his doctorate in chemical engineering from the University of Cambridge. He is a director of Grasim Industries, an Indian-listed company. He has served in advisory roles to the U.S. government and the Republic of Singapore.

Dr. Steven M. Bellovin (NAE) is the Percy K. and Vida L.W. Hudson Professor of Computer Science at Columbia University, a member of the Cybersecurity and Privacy Center of the university's Data Science Institute, and an affiliate faculty member at the Columbia Law School. He performs research on security and privacy and on related public policy issues. Dr. Bellovin received a B.A. from Columbia University and an M.S. and a Ph.D. in computer science from the University of North Carolina

at Chapel Hill. He has served as the chief technologist of the Federal Trade Commission and as a technology scholar at the Privacy and Civil Liberties Oversight Board. He is a member of the National Academy of Engineering and is serving on the Computer Science and Telecommunications Board of the National Academies of Sciences, Engineering, and Medicine. In the past, he has been a member of the U.S. Department of Homeland Security's Science and Technology Advisory Committee and the Technical Guidelines Development Committee of the Election Assistance Commission.

Dr. Patrick M. Boyle is the head of Codebase at Ginkgo Bioworks, a Boston-based synthetic biology company that makes and sells engineered organisms. He is responsible for Ginkgo's Codebase, the company's complete portfolio of reusable biological assets. Codebase includes novel strains, enzymes, genetic parts, and diverse genetic repositories, including millions of engineered DNA sequences. It is being developed, maintained, and leveraged by Ginkgo's organism engineers via dozens of strain-engineering projects. Prior to leading Codebase, Dr. Boyle founded the Design group at Ginkgo, which now produces hundreds of millions of base pairs of DNA designs each year to support Ginkgo's projects. He received an S.B. in biology from the Massachusetts Institute of Technology in 2006. He then received his Ph.D. from the Harvard Medical School in 2012, studying synthetic biology applications in bacteria, yeast, and plants.

Ms. Katherine Charlet was the inaugural director of Carnegie's Technology and International Affairs Program. She works primarily on the security and international implications of evolving technologies, with a focus on cybersecurity and cyber conflict, biotechnology, and artificial intelligence. Ms. Charlet most recently served as the acting deputy assistant secretary of defense for cyber policy, where she managed the development of the U.S. Department of Defense's cyber policy and strategy, the development of cyber capabilities, and the expansion of international cyber relationships. Ms. Charlet is the recipient of the Secretary of Defense Meritorious Civilian Service Award and has served in senior advisory roles on the Defense Science Board Task Forces on Cyber Deterrence, on Cyber as a Strategic Capability, and on the Presidential Commission on Enhancing National Cybersecurity. Prior to working on cyberspace issues, Ms. Charlet served as the director for strategic planning at the National Security Council, led teams at the U.S. Department of Defense working on Afghanistan strategy and policy, and conducted research on issues at the nexus of science and security at the Center for Strategic and International Studies.

Dr. Carol Corrado is the distinguished principal research fellow in economics at The Conference Board and a senior policy scholar at the Center for Business and Public Policy, McDonough School of Business, Georgetown University. Her primary research focus is measuring intangible capital and digital innovation and analyzing their role in economic growth. Dr. Corrado has authored multiple papers on the role of intangible investment and capital in modern economies, including a paper that won the International Association of Research on Income and Wealth's 2010 Kendrick Prize ("Intangible Capital and U.S. Economic Growth"). Her recent work also addresses the measurement of prices for information technology investment goods, consumer digital services, and education services, and an essay on reimagining gross domestic product that she co-authored won the inaugural Indigo Prize in 2017. She received the American Statistical Association's prestigious Julius Shiskin Award for Economic Statistics in 2003 and a Special Achievement Award from the Federal Reserve Board in 1998 for her contributions to measuring high-tech prices and industrial capacity. Dr. Corrado holds a Ph.D. in economics from the University of Pennsylvania and a B.S. in management science from Carnegie Mellon University.

Dr. J. Bradley Dickerson leads the Global Chemical and Biological Security group at Sandia National Laboratories (SNL) in Albuquerque, New Mexico. The GCBS group develops and applies systems-based solutions to reduce the risk of accidental release or intentional misuse of dangerous biological and chemical materials globally. Dr. Dickerson has held numerous leadership positions within the U.S. government, with responsibilities for chemical and biological security. Prior to joining SNL, he served as the principal scientific officer in the U.S. Department of Justice's (DOJ's) National Security Division. Specifically, he served as DOJ's principal science and technical advisor to the Committee on Foreign Investment in the United States. Prior to that, Dr. Dickerson served as the senior biodefense advisor in the U.S. Department of Homeland Security's (DHS's) Office of Health Affairs and as the director of chemical security policy in DHS's Office of Policy. At DHS he was responsible for the development and implementation of policies associated with biodefense, chemical defense, pandemic preparedness, and infectious disease–related border issues. Dr. Dickerson completed a detail at the U.S. Centers for Disease Control and Prevention (CDC), where he led the policy and strategy component of the Office of Public Health Preparedness and Response, which comprises the CDC Division of Emergency Operations, Division of State and Local Readiness, Division of Select Agents and Toxins, and Division of the Strategic National Stockpile. He was awarded a Legis Congressional Fellowship from the Brookings Institution and the American Association for the

Advancement of Science's National Defense and Global Security Policy Fellowship. Dr. Dickerson holds a B.S. in chemistry, an M.S. in biomedical engineering, and a Ph.D. in biochemistry.

Dr. Diane DiEuliis is a senior research fellow at the National Defense University (NDU). Her research focuses on emerging biological technologies, biodefense, and preparedness for biothreats. Dr. DiEuliis also studies issues related to dual-use research; disaster recovery; and behavioral, cognitive, and social science as it relates to important aspects of deterrence and preparedness. Prior to joining NDU, Dr. DiEuliis was the deputy director for policy in the Office of the Assistant Secretary for Preparedness and Response, U.S. Department of Health and Human Services. She also previously served in the Office of Science and Technology Policy at the White House and was a program director at the National Institutes of Health. She has broad knowledge of the policy implications of emerging technologies, as well as the intricacies that accompany the institution of new policies to regulate such technologies. Dr. DiEuliis received her Ph.D. in biological sciences from the University of Delaware.

Dr. Gerald Epstein is a distinguished research fellow with the Center for the Study of Weapons of Mass Destruction at the National Defense University. He works at the intersection of science, technology, and security policy, particularly concerning the governance and security implications of advanced life sciences, biotechnologies, and other emerging and converging technologies. Previously, he served at the White House Office of Science and Technology (OSTP) as the assistant director for biosecurity and emerging technologies, a position he held on detail from his U.S. Department of Homeland Security (DHS) appointment as deputy assistant secretary for chemical, biological, radiological, and nuclear policy. Before joining DHS, Dr. Epstein held positions with the American Association for the Advancement of Science, the Center for Strategic and International Studies, the Institute for Defense Analyses, and the Congressional Office of Technology Assessment. He directed a project on the relationship between military and commercial technologies at Harvard University, and he has taught at Princeton University and Georgetown University. In a prior White House appointment, he served jointly as the assistant OSTP director for national security and the senior director for science and technology on the National Security Council staff. He holds S.B. degrees in physics and electrical engineering from the Massachusetts Institute of Technology and M.S. and Ph.D. degrees in physics from the University of California, Berkeley.

Dr. Steven L. Evans is a recently retired research fellow from Dow AgroSciences, which is now part of Corteva Agriscience. He has 30 years of experience in discovery research and development, biotechnology regulation, and commercialization of crop traits and biological and biochemical pesticides. For the past 10 years, he has worked to advance the field of synthetic biology in public–private partnerships. He served in industrial leadership on the National Science Foundation's Synthetic Biology Engineering Research Center and is currently on the executive leadership team of the successor nonprofit Engineering Biology Research Consortium in Emeryville, California. He co-chaired the BIO Synthetic Biology working group until 2018 and is involved in technology and policy implications of advanced technologies applied to agriculture, including environmental release, biosafety, and biosecurity, and the United Nations Convention on Biodiversity's assessment of synthetic biology. As part of Dow AgroSciences, Dr. Evans has been involved in the development of several plant traits leading to the Herculex™ product line, in capability development in bioanalytical sciences, and in enabling the EXZACT™ Zinc Finger technology. He served on the 2016 National Academies' Committee on Future Biotechnology Products and Opportunities to Enhance Capabilities of the Biotechnology Regulatory System.

Dr. George B. Frisvold is currently a professor and an extension specialist in the Department of Agriculture and Resource Economics at the University of Arizona. He has been a visiting scholar at the National Institute of Rural Development in Hyderabad, India; a lecturer at Johns Hopkins University; and the chief of the Resource and Environmental Policy Branch of the U.S. Department of Agriculture's Economic Research Service. His research interests include domestic and international environmental policy, as well as the causes and consequences of technological change in agriculture. In 1995–1996, Dr. Frisvold served on the senior staff of the President's Council of Economic Advisers, with responsibility for agricultural, natural resource, and international trade issues. He is an associate editor for the journals *Pest Management Science* and *Water Economics and Policy*. Dr. Frisvold earned his B.S. in political economy of natural resources in 1983 and his Ph.D. in agricultural and resources economics in 1989, both from the University of California, Berkeley.

Dr. Jeffrey L. Furman is an associate professor of strategy and innovation at Boston University and a research associate at the National Bureau of Economic Research (NBER). His research addresses issues in innovation, science policy, and the strategic management of science-based firms. His research has been published in a range of leading academic journals, including the *American Economic Review*, the *Review of Economics*

and Statistics, *Organization Science*, *Research Policy*, and *Nature*. Recent projects involve investigating the impact of institutions on cumulative innovation, the strategic management of science-based enterprises, and science and innovation policy. Dr. Furman co-organizes NBER's Productivity Seminar, and recently completed separate terms as a member of the Executive Committee of the Academy of Management's Strategy Division and Technology & Innovation Division and a 6-year term as the academic director of the undergraduate program at Boston University's Questrom School of Business. Dr. Furman received his Ph.D. from the Massachusetts Institute of Technology's Sloan School of Management and completed undergraduate degrees from the University of Pennsylvania's College of Arts and Science and Wharton School of Business.

Dr. Linda Kahl is a dedicated and experienced advocate for biotechnology in the public interest. She is the founder and principal of SciScript Communications, a consulting firm providing strategic planning and scientific writing services to biotechnology companies, government agencies, nonprofit organizations, universities, and research institutes in the areas of biomarker discovery, cancer research, genomics, infectious and chronic disease, medical economics, molecular diagnostics, and synthetic biology. Dr. Kahl also maintains a law practice as counsel with Perspectives Law Group and is a licensed patent attorney with bar admission to practice law in California and before the U.S. Patent and Trademark Office. She formerly served as the senior counsel for the BioBricks Foundation, where she led development of the Open Material Transfer Agreement. Dr. Kahl has been appointed as a Herbert Smith Freehills Visiting Scholar at the University of Cambridge Faculty of Law, a policy fellow at the University of Cambridge Centre for Science and Policy, and a visiting research fellow at Stanford University. Originally trained as a research scientist, she received her B.S. in biology from the University of California, Los Angeles, and her M.S. and Ph.D. in cell biology and biochemistry from Princeton University. Dr. Kahl received her J.D. magna cum laude from the Santa Clara University School of Law, earning the High Tech Law Certificate with an emphasis in intellectual property law.

Dr. Isaac S. Kohane (NAM) is currently the chair of the Department of Biomedical Informatics at Harvard University. Over the past 30 years, his research agenda has been driven by the vision of what biomedical researchers could do to find new cures, provide new diagnoses, and deliver the best care available if data could be converted more rapidly to knowledge and knowledge to practice. Dr. Kohane has designed and led multiple internationally adopted efforts to "instrument" the health care enterprise for discovery and to enable innovative decision-making tools

to be applied to the point of care. He has worked on recharacterizing and reclassifying such diseases as autism, rheumatoid arthritis, and cancers. In many of these studies, the developmental trajectories of thousands of genes have been a powerful tool in unraveling complex diseases.

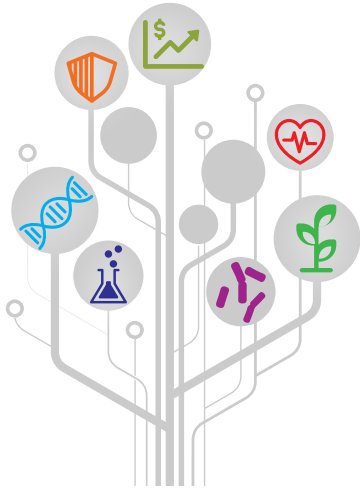
Dr. Kelvin H. Lee is the Gore Professor of Chemical and Biomolecular Engineering at the University of Delaware. He currently serves as the director of the National Institute for Innovation in Manufacturing Biopharmaceuticals (a Manufacturing USA Institute) and he previously served as the director of the Delaware Biotechnology Institute. Dr. Lee received a B.S.E. in chemical engineering from Princeton University and both his M.S. and Ph.D. in chemical engineering from Caltech. He also completed a postdoc in Caltech's Biology Division and spent several years at the Biotechnology Institute at the ETH in Zurich, Switzerland. Previously, he was on the faculty at Cornell University where he held the titles of Samuel C. and Nancy M. Fleming Chair Professor, professor in the School of Chemical and Biomolecular Engineering, director of the Cornell Institute for Biotechnology, and director of the New York State Center for Life Science Enterprise. He is a fellow of the American Association for the Advancement of Science and of the American Institute for Medical and Biological Engineers. His research expertise is in systems and synthetic biology applied to biopharmaceutical manufacturing as well as in the diagnosis and treatment of Alzheimer's disease.

Dr. Mary E. Maxon is the associate laboratory director for biosciences at the Berkeley National Laboratory. She oversees the laboratory's biological systems and engineering, environmental genomics and systems biology, and molecular biophysics and integrated bioimaging divisions and the Department of Energy Joint Genome Institute. Dr. Maxon earned her B.S. in biology and chemistry from the State University of New York, Albany, and her Ph.D. in molecular cell biology from the University of California, Berkeley. She has worked in the private sector in both the biotechnology and pharmaceutical industries, as well as in the public sector. Her public-sector service was highlighted by her tenure as the assistant director for biological research at the White House Office of Science and Technology Policy in the Executive Office of the President, where she developed the National Bioeconomy Blueprint.

Dr. Maureen McCann is a professor of biological sciences at Purdue University, the president-elect of the American Society of Plant Biology, and the director of Purdue's NEPTUNE Center for Power and Energy, funded by the Office of Naval Research. The goal of her research is to understand how the molecular machinery of the plant cell wall contributes to

cell growth and specialization, and thus to the final stature and form of plants. She currently serves on the U.S. Department of Energy's (DOE's) Biological and Environmental Remediation Advisory Committee and has previously served on the U.S. Department of Agriculture–DOE Biomass Research and Development Technical Advisory Committee and the DOE Office of Science, Council for Chemical and Biochemical Sciences. In 2018–2019, Dr. McCann participated, as 1 of 14 nominated individuals, in DOE's Oppenheimer Science and Energy Leadership Program to provide future leaders with an overview of DOE and the National Laboratory system. From 2009 to 2018, she was the director of the Center for Direct Catalytic Conversion of Biomass to Biofuels (C3Bio), an Energy Frontier Research Center funded by DOE's Office of Science. Within C3Bio, Dr. McCann's lab explored synthetic biology and genetic engineering approaches to optimize cell wall and biomass structure for chemical conversion processes. She also served as the director of Purdue University's Energy Center, representing more than 200 affiliated faculty with energy-related research interests. Prior to joining the faculty at Purdue, she was a project leader at the John Innes Centre Norwich in the United Kingdom, a government-funded research institute for plant and microbial sciences, funded by The Royal Society with a University Research Fellowship. She received her undergraduate degree in natural sciences from the University of Cambridge and a Ph.D. in botany from the University of East Anglia in the United Kingdom.

Dr. Piers D. Millett is the director of safety and security at iGEM and co-chairs iGEM's Safety Committee. He is a certified biorisk management professional, with a specialization in biosecurity. Until June 2014, Dr. Millett was the deputy head of the Implementation Support Unit for the Biological Weapons Convention, a treaty for which he worked for more than a decade. Trained originally as a microbiologist, he is a chartered biologist and works closely with the citizen science movement, synthetic biologists, and the biotechnology industry, as well as governments. He has collaborated with a range of intergovernmental organizations spanning health (human and animal), humanitarian law, disarmament, security, border control, law enforcement, and weapons of mass destruction—both inside and outside of the United Nations system. Dr. Millett also co-founded a consultancy firm that works with government, industry, and academia to ensure the safe, secure, and sustainable exploitation of biology as a manufacturing technology. He holds fellowships with the Future of Humanity Institute at the University of Oxford and the Woodrow Wilson Center for International Scholars in Washington, DC, where he researches pandemic and deliberate disease and the implications of biotechnology. He also consults for the World Health Organization, supporting its research and development efforts.



B
INVITED SPEAKERS

The following individuals were invited speakers at meetings and data-gathering sessions of the committee:

Denise Anderson
National Health Information Sharing and Analysis Center

Jeff Baker
U.S. Food and Drug Administration

Kavita Berger
Gryphon Scientific, LLC

Patrick Boyle
Ginkgo BioWorks

Atul Butte
University of California, San Francisco

Rob Carlson
Bioeconomy Capital

Nick Carruthers
Janssen Research & Development

John Cumbers
SynBioBeta

Julia Doherty
Office of the United States Trade Representative

Mary Edwards
Office of the Director of National Intelligence

Sam Weiss Evans
Tufts University

Maryann Feldman
University of North Carolina

Daniel Flynn
Office of the Director of National Intelligence

Avi Goldfarb
University of Toronto

Peter Harrell
Center for a New American Security

James Hayne
PhRMA

Corey Hudson
Sandia National Laboratory

Mark Kazmierczak
Gryphon Scientific, LLC

Jan Koninckx
DuPont Industrial Biosciences

Gene Lester
U.S. Department of Agriculture

Nicolas Federico Martin
University of Illinois at Urbana-Champaign

Alexa T. McCray
Harvard Medical School

Randall Murch
Virginia Tech University

Kimberly Orr
Bureau of Industry and Security

Eleonore Pauwels
United Nations University Centre for Policy Research

Ben Petro
U.S. Department of Defense

Daniel Rock
Massachusetts Institute of Technology

Larisa Rudenko
Massachusetts Institute of Technology

Diane L. Souvaine
Tufts University

David Spielman
International Food Policy Research Institute

Debra K. Stanislawski
Office of the Director of National Intelligence

Scott Stern
Massachusetts Institute of Technology

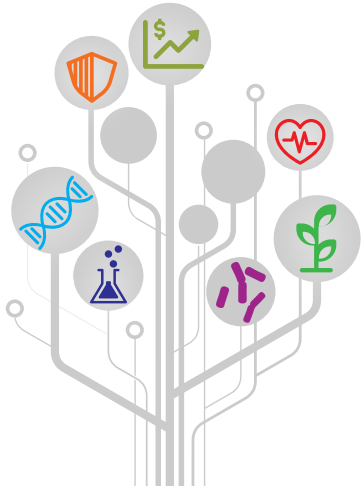
William Sutherland
University of Cambridge

Michael Tarlov
National Institute of Standards and Technology

Ian Watson
Office of Science and Technology Policy

Sharlene Weatherwax
U.S. Department of Energy

Edward H. You
Federal Bureau of Investigation



C
PARTICIPATING BOARDS

BOARD ON LIFE SCIENCES

JAMES P. COLLINS, *Chair*, Arizona State University
A. ALONSO AGUIRRE, George Mason University
ENRIQUETA C. BOND, Burroughs Wellcome Fund
DOMINIQUE BROSSARD, University of Wisconsin–Madison
ROGER D. CONE, University of Michigan
NANCY D. CONNELL, Johns Hopkins Center for Health Security
SEAN M. DECATUR, Kenyon College
JOSEPH R. ECKER, Salk Institute for Biological Studies
SCOTT V. EDWARDS, Harvard University
GERALD L. EPSTEIN, National Defense University
ROBERT J. FULL, University of California, Berkeley
ELIZABETH HEITMAN, University of Texas Southwestern Medical Center
MARY E. MAXON, Lawrence Berkeley National Laboratory
ROBERT NEWMAN, Independent Consultant
STEPHEN J. O'BRIEN, Nova Southeastern University
CLAIRE POMEROY, Albert and Mary Lasker Foundation
MARY E. POWER, University of California, Berkeley
SUSAN RUNDELL SINGER, Rollins College
LANA SKIRBOLL, Sanofi
DAVID R. WALT, Harvard Medical School

Staff

FRANCES SHARPLES, Director
KATIE BOWMAN, Senior Program Officer
ANDREA HODGSON, Program Officer
JO HUSBANDS, Senior Scholar
KEEGAN SAWYER, Senior Program Officer
AUDREY THEVENON, Program Officer
STEVEN M. MOSS, Associate Program Officer
JESSICA DE MOUY, Senior Program Assistant
KOSSANA YOUNG, Senior Program Assistant

BOARD ON AGRICULTURE AND NATURAL RESOURCES

CHARLES W. RICE, *Chair,* Kansas State University
SHANE C. BURGESS, University of Arizona
SUSAN M. CAPALBO, Oregon State University
GAIL L. CZARNECKI-MAULDEN, Nestlé Purina Pet Care
GEBISA EJETA, Purdue University
JAMES S. FAMIGLIETTI, University of Saskatchewan
FRED GOULD, North Carolina State University
DOUGLAS B. JACKSON-SMITH, The Ohio State University
JAMES W. JONES, University of Florida
STEPHEN S. KELLEY, North Carolina State University
JAN E. LEACH, Colorado State University
JILL J. McCLUSKEY, Washington State University
KAREN I. PLAUT, Purdue University
JIM E. RIVIERE, Kansas State University

Staff

ROBIN SCHOEN, Director
KARA LANEY, Senior Program Officer
CAMILLA YANDOC ABLES, Senior Program Officer
JENNA BRISCOE, Research Associate
SARAH KWON, Program Assistant

BOARD ON SCIENCE, TECHNOLOGY, AND ECONOMIC POLICY

ADAM B. JAFFE, *Chair,* Brandeis University
NOEL BAKHTIAN, Idaho National Laboratory
JEFF BINGAMAN, U.S. Senate (retired)
BRENDA J. DIETRICH, Cornell University

BRIAN G. HUGHES, HBN Shoe, LLC
ADRIANNA KUGLER, Georgetown University
ARATI PRABHAKAR, Defense Advanced Research Projects Agency (retired)
KATHRYN L. SHAW, Stanford University
SCOTT STERN, Massachusetts Institute of Technology
JOHN C. WALL, Cummins, Inc. (retired)

Staff

GAIL E. COHEN, Executive Director
DAVID DIERKSHEIDE, Program Officer
ANITA EISENSTADT, Program Officer
STEVEN KENDALL, Program Officer
FRED LESTINA, Research Associate
CLARA SAVAGE, Financial Officer

BOARD ON HEALTH SCIENCES POLICY

JEFFREY KAHN, *Chair,* Johns Hopkins University
DAVID BLAZES, Bill & Melinda Gates Foundation
ROBERT CALIFF, Duke University
ARAVINDA CHAKRAVARTI, New York University
R. ALTA CHARO, University of Wisconsin–Madison
LINDA HAWES CLEVER, California Pacific Medical Center
BARRY S. COLLER, The Rockefeller University
BERNARD A. HARRIS, Vesalius Ventures
MARTHA N. HILL, Johns Hopkins University School of Nursing
FRANCES E. JENSEN, University of Pennsylvania Perelman School of Medicine
PATRICIA A. KING, Georgetown University Law Center
STORY C. LANDIS, National Institute of Neurological Disorders and Stroke
FRANK R. LIN, Johns Hopkins Cochlear Center for Hearing and Public Health
SUZET M. McKINNEY, Illinois Medical District
BRAY PATRICK-LAKE, Duke Clinical Research Institute
LYNNE D. RICHARDSON, Mount Sinai Health System
DIETRAM SCHEUFELE, University of Wisconsin–Madison
UMAIR A. SHAH, Harris County Public Health
ROBYN I. STONE, LeadingAge
SHARON TERRY, Genetic Alliance

Staff

ANDREW M. POPE, Senior Board Director
SCOTT WOLLEK, Senior Program Officer
MARIAM SHELTON, Research Associate

FORUM ON CYBER RESILIENCE

DR. FRED SCHNEIDER, *Chair,* Cornell University
YAIR AMIR, Johns Hopkins University
BOB BLAKLEY, Citigroup
FRED CATE, Indiana University
KATHERINE CHARLET, Carnegie Endowment for International Peace
DAVID CLARK, Massachusetts Institute of Technology
RICHARD DANZIG, Center for a New American Security
ERIC GROSSE, Independent Consultant
PAUL KOCHER, Cryptography Research, Inc.
BUTLES LAMPSON, Microsoft Corporation
SUSAN LANDAU, Tufts University
JOHN LAUNCHBURY, Galois, Inc.
STEVEN B. LIPNER, Independent Consultant
JOHN MANFERDELLI, Northeastern University
DEIRDRE K. MULLIGAN, University of California, Berkeley
AUDREY PLONK, Intel Corporation
TONY SAGER, Center for Internet Security
PETER SWIRE, Georgia Institute of Technology
PARISA TABRIZ, Google, Inc.
MARY ELLEEN ZURKO, Massachusetts Institute of Technology Lincoln Laboratory

Staff

LYNETTE I. MILLETT, Director
KATIRIA ORTIZ, Associate Program Officer