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The Role of NIH in Drug Development Innovation and Its Impact on Patient Access

PROCEEDINGS OF A WORKSHOP

Francis K. Amankwah, Alexandra Andrada, Sharyl J. Nass, and Theresa Wizemann, *Rapporteurs*

Board on Health Care Services

Board on Health Sciences Policy

Health and Medicine Division

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National Academies and that all review comments were carefully considered. Responsibility for the final content rests entirely with the rapporteurs and the National Academies.

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Acronyms and Abbreviations

ASP	average sales price
BARDA	Biomedical Advanced Research and Development Authority
CAP	cross-agency priority
CAR-T	chimeric antigen receptor T-cell
CARB-X	Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator
cDNA	complementary DNA
CMS	Centers for Medicare & Medicaid Services
CRADA	cooperative research and development agreement
CTSA	Clinical and Translational Science Awards
DoD	U.S. Department of Defense
EHR	electronic health record
ERP	external reference pricing
FDA	U.S. Food and Drug Administration
gDNA	genomic DNA

HCV	hepatitis C virus
HHS	U.S. Department of Health and Human Services
I-MAK	Initiative for Medicines, Access, & Knowledge, Inc.
iPSC	induced pluripotent stem cell
IRB	institutional review board
L2M	Lab-to-Market
MeSH	Medline Subject Headings
NCATS	National Center for Advancing Translational Sciences
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NIST	National Institute of Standards and Technology (U.S. Department of Commerce)
PBM	pharmacy benefit manager
PDUFA	Prescription Drug User Fee Act
PI	principal investigator
PrEP	pre-exposure prophylaxis
R&D	research and development
ROI	return on investment
SBIR	Small Business Innovation Research program
SNS	Strategic National Stockpile
STTR	Small Business Technology Transfer program
UAEM	Universities Allied for Essential Medicines
USPTO	U.S. Patent and Trademark Office

Proceedings of a Workshop

OVERVIEW OF THE WORKSHOP

Prescription drug expenditures now account for nearly 17 percent of personal health care spending in the United States (ASPE, 2016; NASEM, 2018). Prescription drug prices continue to increase and paying for prescription medicines has become a significant concern for many Americans. There are many different perspectives on what constitutes "value" as it relates to health care, defined as health outcomes achieved per dollar spent. However, as concluded in a recent consensus study report from the National Academies of Sciences, Engineering, and Medicine, *Making Medicines Affordable: A National Imperative*, "there is little value in new drugs that patients cannot afford—and there is no value in drugs that do not exist" (NASEM, 2018, p. 125). The report offered numerous policy solutions for improving patient access to affordable medicines, but thus far, unified national action has not emerged. Pharmaceutical manufacturers retain the ability to set prices based on "what the market will bear" for their products. Pharmacy benefit managers have the ability to partially negotiate prices, but it is often not clear how much of those savings are passed down to patients. In addition, some public payers, such as Medicare, are prohibited by law from negotiating prices.

Bringing safe and effective new medicines to market is a lengthy, high-cost, and high-risk enterprise. Pharmaceutical developers have raised concerns that attempts to control drug prices could stifle investment and

innovation in new drug development, with potentially serious implications for health outcomes. However, the private sector does not necessarily bear the full cost of drug development.

Public funding appropriated to the National Institutes of Health (NIH) to support extramural and intramural biomedical research contributes directly and indirectly to innovative drug discovery and development. The extent of this contribution is not well characterized and is difficult to measure, but recent studies suggest a direct link between NIH funding and important new drugs. Taxpayer dollars fund NIH and therefore fund the research done by NIH scientists and grantees that drive new drug development and commercialization in the private sector. A continuous issue is whether we can and should implement policy solutions that would ensure the affordability of drugs developed with support of taxpayer dollars.

To explore the role of NIH in innovative drug development and its impact on patient access, the Board on Health Care Services and the Board on Health Sciences Policy of the National Academies jointly hosted a public workshop on July 24–25, 2019, in Washington, DC. The workshop was sponsored by the Laura and John Arnold Foundation (now Arnold Ventures). An ad hoc committee[1] was appointed to invite individuals with a range of expertise and experiences, including basic and translational biomedical research, drug development and commercialization, health economics, research funding, patient advocacy, health care policy, and science policy to speak at the workshop and participate in the discussions.

Jeff Bingaman, former U.S. Senator from New Mexico and chair of the workshop planning committee, opened the workshop by emphasizing that "patient access to innovative drugs continues to be a serious topic of public and policy interests." Workshop speakers and participants discussed the ways in which federal investments in biomedical research are translated into innovative therapies and considered approaches to ensure that the public has affordable access to the resulting new drugs. Appendixes A and

[1] The planning committee's role was limited to planning the workshop, and the Proceedings of a Workshop was prepared by the workshop rapporteurs as a factual summary of what occurred at the workshop. Statements, recommendations, and opinions expressed are those of individual presenters and participants, and are not necessarily endorsed or verified by the National Academies of Sciences, Engineering, and Medicine, and they should not be construed as reflecting any group consensus.

B present the workshop Statement of Task and agenda, respectively.[2] The objectives of the workshop were to discuss:

- how federal funding for biomedical research, particularly via NIH, has contributed to new drug development, both directly and indirectly;
- the pricing of drugs that have benefited from federal investments in biomedical science;
- the role of technology transfer to and from entrepreneurial organizations associated with NIH-funded research;
- potential ways to better track, quantify, and document NIH contributions to innovation in drug development; and
- potential strategies and policies to facilitate the translation of federally funded biomedical research into innovations in drug development and to help ensure that the public has affordable access to those innovative medicines.

This proceedings summarizes the presentations and discussions that took place at the workshop. Highlights of observations and suggestions from the individual presentations and discussions are presented in Box 1 and discussed in the proceedings.

THE TRANSLATIONAL RESEARCH LANDSCAPE

To set the stage for the workshop discussions, Christopher Austin, director of the National Center for Advancing Translational Sciences (NCATS) at NIH/U.S. Department of Health and Human Services (HHS), provided an overview of the translational research landscape (defined in Box 2). He reminded participants that part of the NIH mission is to conduct and support research that will eventually lead to therapeutic interventions. NIH does not have a role in drug pricing. Austin said the "cost of production and price are inexactly related." He added that NIH hopes to be able to impact the cost of the drug development production process through its

[2] Archived webcast videos and speakers' presentations are available on the National Academies website. See http://nationalacademies.org/hmd/Activities/HealthServices/RoleofNIHinDrugDevelopmentInnovationandItsImpactonPatientAccess/2019-JUL-24.aspx (accessed September 23, 2019).

BOX 1
Observations and Suggestions Made by Individual Workshop Participants

The Translational Research Landscape

- Perspectives of the translational research landscape and associated challenges vary considerably among the many diverse stakeholders. (Austin)
- The role of translational science is to develop innovative new methods and technologies that can increase efficiency and decrease failure, making drug development a more predictable process. (Austin)
- Translational science requires a team effort. (Austin, Woodcock)
- Translational science is not prioritized as a field of study. In academia, translational science is not rewarded (e.g., with promotion or tenure) and is underfunded. (Austin, Stevens, Woodcock)

The Role of Federally Funded Biomedical Research

- "The National Institutes of Health [NIH] enterprise is necessary" for the advancement of product development, but "it is not sufficient." (Woodcock)
- Ten percent of all drugs, and 20–30 percent of priority review, first-in-class, or top-selling drugs, can be directly linked to publicly funded research. (Sampat)
- There is evidence of spillovers of NIH funding to private-sector drug developers, and fewer drugs would be developed in the absence of NIH funding. (Li)
- Early-stage basic biomedical research is generally a high-risk investment, and it is public funding that takes on this risk and supports these endeavors. (Kesselheim)

Patent and Technology Transfer Issues

- The intended meaning of "available to the public on reasonable terms" in the march-in rights provision of the Bayh-Dole Act has been the subject of much debate, particularly over who is considered "the public" (e.g., the licensee, the payer, the end user), and whether "reasonable terms" includes pricing. (Na, Rai, Stevens, Thomas)
- Concerns that the reasonable pricing clause previously used in NIH cooperative research and development agreements (CRADAs) had a "chilling" effect on cooperation are unfounded. (Kesselheim, Mitchell)

- No federal agency has ever exercised its "march-in rights." Attempts to use "march-in rights" to influence pricing are not practical, are unlikely to be effective (Kesselheim, Stevens, Thomas), and could be counter-productive. (Stevens)

Drug Pricing, Access, and Affordability

- Drugs are not effective if people cannot afford them. (Austin, Kesselheim, Mitchell)
- New drugs can be cost-effective and still be unaffordable to many people. (Chandra, Sampat)
- Cost is not the basis for price. Pricing is reflective of the value to the buyer or their "willingness to pay." Pricing is also reflective of insurance reimbursement plans that are not designed to constrain price. A system of rebates creates a competitive market for many small molecule drugs but does not work well for specialty drugs. (Danzon)
- NIH is focused on conducting and collaborating on cutting-edge science to meet the health needs of the nation. NIH does not and should not have the responsibility for pricing. (Mitchell)
- Consumers have limited awareness of their role as taxpayers in funding research and development of pharmaceutical products. (Purvis)
- The current approach to drug pricing is unsustainable for payers or the public and unfair to the public whose taxes fund biomedical research. (Kesselheim, Mitchell, Purvis)

Facilitating Translation of Federally Funded Biomedical Research

- Establish public–private partnerships, precompetitive collaborations, and research consortia to address efficiency issues in drug development. (Carino, Colvis, Dilts, Galson, Hudson)
- Consider partnering with the U.S. Department of Defense (DoD) on areas of common interest. A significant amount of the DoD funding is dedicated to competitive extramural grants. (Rauch)
- Address efficiency "holistically" at a systems level, identifying the role and responsibility of each stakeholder to form more productive collaborations. (Dilts)
- Create precompetitive consortia to develop standards and reduce the variance at each step of the drug development process to increase overall efficiency. (Dilts)
- Engage project management professionals and systems engineers to manage the collaborative process and allow the biomedical experts to focus on the science. (Colvis, Dilts)

continued

BOX 1 Continued

- Leverage new technologies and process improvements to help increase rates of success and reduce costs in drug development. (Galson)
- Use novel trial designs, such as platform trials, to increase efficiency. (Woodcock)
- Repurpose existing approved products for secondary uses. (Colvis)
- Increase funding for NIH to support basic translational science studies. (Hudson)
- Facilitate patient enrollment in clinical research, such as making clinical trial information easier to navigate and understand. (Carino)

Ensuring Affordable Access to Drugs That Have Benefited from Federal Funding

- Address pricing at the point of technology transfer. (Mitchell)
- Create a separate entity to negotiate the pricing aspect of intellectual property transfer. (Mitchell, Sarpatwari) This could be within the U.S. Department of Health and Human Services. (Merrill)
- Reinstate the reasonable pricing provision in CRADAs and exclusive licensing agreements. (Kesselheim, Mitchell)
- Reform the patent system, including modifying the inventiveness standards for patents, restricting continuation applications, and improving the existing challenge system. (Amin)
- Improve tracking of the patents and intellectual property that result from taxpayer-funded research (Mitchell), monitor the disclosure of federal funding in patents more strictly, and implement penalties for lack of disclosure. (Amin)

research mission. He added that HHS is working to address the rising cost of prescription drugs directly and has developed a blueprint for action.[3]

One's perspective on the translational research landscape is shaped, and sometimes limited, by where one operates within the drug development ecosystem, Austin said. This ecosystem includes NIH, both employees and grantees; academic researchers; patients, some of whom are also advocates and entrepreneurs; venture capital organizations; biotechnology companies;

[3] See https://www.hhs.gov/about/leadership/secretary/priorities/drug-prices/index.html (accessed September 23, 2019).

- Utilize existing authorities under current law (e.g., Bayh-Dole Act provisions, 28 U.S.C. Section 1498). (Kesselheim)
- Legislate general drug pricing and access reform, looking to other countries for models. (Kesselheim)
- Explore the possibility of expanded public funding of clinical trials and later-phase product development. (Kesselheim, Sampat) Government could expand support for development in areas of urgent need but for which profits are limited and investment interest is low (e.g., antibiotics). (Carino, Mitchell)
- Increase consumer (i.e., taxpayer) awareness and engagement on pricing issues. (Purvis)
- Explore a range of potential models for addressing affordable drug access.
  - Link NIH funding to value, not price. NIH funding could be linked to a value-based pricing framework (e.g., pricing at a specific value-for-money threshold), providing an appropriate return on investment for publicly funded and subsidized biomedical research and rewarding the private sector for increasing product value. (Danzon)
  - Delink profit from volume sold. A "subscription model" for pricing would achieve this and reward products of greater societal value. For example, the federal government would pay a fixed, value-based, price per year for access to a company's antibiotics, regardless of level of use. (Outterson)
  - Explore a "cost-of-cure approach" to funding drug development. The costs of large-scale access to specialty drugs could potentially be offset over time by the reduced use of health care. (Wirth)

pharmaceutical companies; regulators, including the U.S. Food and Drug Administration (FDA); and payers, including the Centers for Medicare & Medicaid Services (CMS). He said that participants within the ecosystem will come to the discussions with very different but equally valid points of view. Austin also observed what he described as an "asymmetry of knowledge." He said that people in pharmaceutical research and development (R&D) have experience in an academic organization and understand how academic research is conducted. In contrast, he said, most people in academia have little to no exposure to what is involved in the development of a new therapeutic.

BOX 2
Definitions

- "***Translation*** is the process of turning observations in the laboratory, clinic, and community into interventions that improve the health of individuals and the public, from diagnostics and therapeutics to medical procedures and behavioral changes."
- "***Translational science*** is the field of investigation focused on understanding the scientific and operational principles underlying each step of the translational process."
- "***Translational research*** endeavors to traverse a particular step of translation for a particular target or disease."

SOURCES: Austin presentation, July 24, 2019; Austin, 2018.

Bridging the Valley of Death

The "Valley of Death" is often used to describe the gap between basic drug discovery research and the development of a therapeutic product that can be delivered to patients. Austin noted that this moniker stems from the "extreme difficulty and likelihood of failure" of most attempts to translate a finding from bench to bedside. He explained that NCATS is focused on eliminating the Valley of Death with translational science, making the translational process more predictable and "transversable" and thereby increasing the likelihood of success.

Austin mentioned that an action collaborative,[4] an ad hoc-activity associated with the National Academies' Forum on Drug Discovery, Development, and Translation[5] (of which Austin is a member), mapped the complexities of the drug development process to better navigate this gap, diagramming the many potential handoffs between sectors. He stressed that the traditional "pipeline" analogy for the drug development process was too simplistic and did not accurately convey the intricacies of the translational process. He explained that the collaborative took a crowdsourcing approach and created detailed maps to educate stakeholders and aid in engineering improvements

[4] See http://nationalacademies.org/hmd/Activities/Research/DrugForum/Mapping-and-Connecting.aspx (accessed September 23, 2019).

[5] See http://nationalacademies.org/hmd/activities/research/drugforum.aspx (accessed September 23, 2019).

across the breadth of the processes for both small molecules and biologics (Wagner et al., 2018a,b). Static versions of the maps provide an overview of the interdependent steps across the processes (see Figure 1). Newer dynamic versions, publicly available on the NCATS website, allow users to expand each sector to view the multiple potential interactions, or "traffic," among the sectors and access related resources and NCATS programs.[6]

Austin described the current state of therapeutic development as a "remarkably bittersweet time." He noted that there have been remarkable advances in basic and clinical science (e.g., the human genome project, induced pluripotent stem cells [iPSCs]), but translating the science into tangible health improvements has not consistently followed the development of interventions and remains "failure-prone, inefficient, and costly." He referred participants to the 2013 report *U.S. Health in International Perspective: Shorter Lives, Poorer Health* for additional background (NRC and IOM, 2013) and highlighted that the "enormous, unprecedented opportunity" to address health problems given the state of the science is now. As an example, Austin said, the number of human conditions for which the molecular basis is known (e.g., the genes for cystic fibrosis, Huntington's disease, and sickle cell disease have been identified) has increased dramatically over the past three decades. However, of these nearly 6,500 diseases, only about 500 have treatments available. In other words, "95 percent of human diseases have no treatment," he said.

Eroom's Law

On average, the end-to-end drug development process currently takes about 15 years. This suggests a corresponding increase in the number of drugs available "if we just wait 15 years." Austin reiterated that the advances in basic and clinical science are not reflected in the number of new products reaching patients and acknowledged that this is not due to a lack of effort, but challenges that are very difficult to overcome. This difficulty is reflected in Eroom's Law (see Figure 2), which is Moore's Law[7] spelled backward.

[6] Static images of the 4DM Maps for small molecules and biologics are available from NCATS at https://ncats.nih.gov/translation/maps (accessed September 23, 2019). Interactive maps of each area of the process are available at https://4dmap.ncats.nih.gov/# (accessed September 23, 2019).

[7] Moore's Law, named after Gordon Moore, one of the founders of Intel, states that the number of transistors that can fit on a microprocessor doubles about every 2 years. This increase in computer speed/processing power has been associated with a decrease in cost (see Moore, 1965).

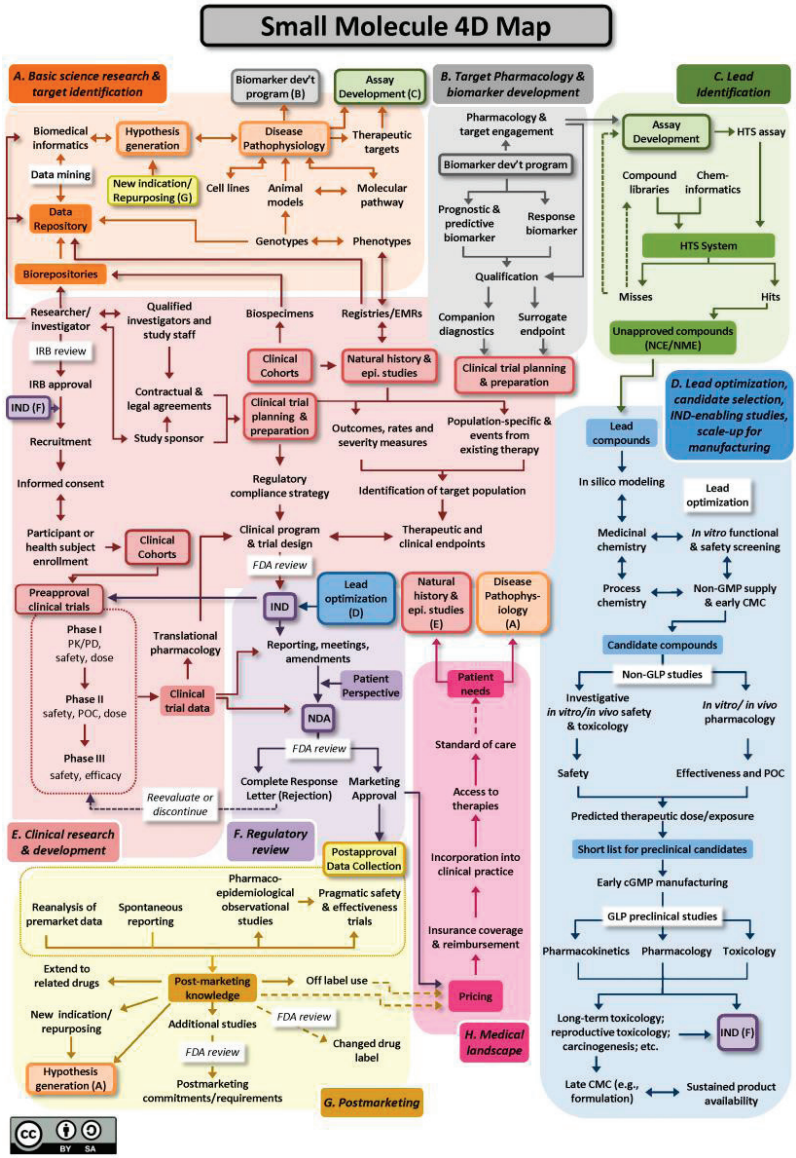

FIGURE 1 Drug discovery, development, and deployment map (4DM) for small molecules and biologics.

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SOURCES: Austin presentation, July 24, 2019; Wagner et al., 2017.

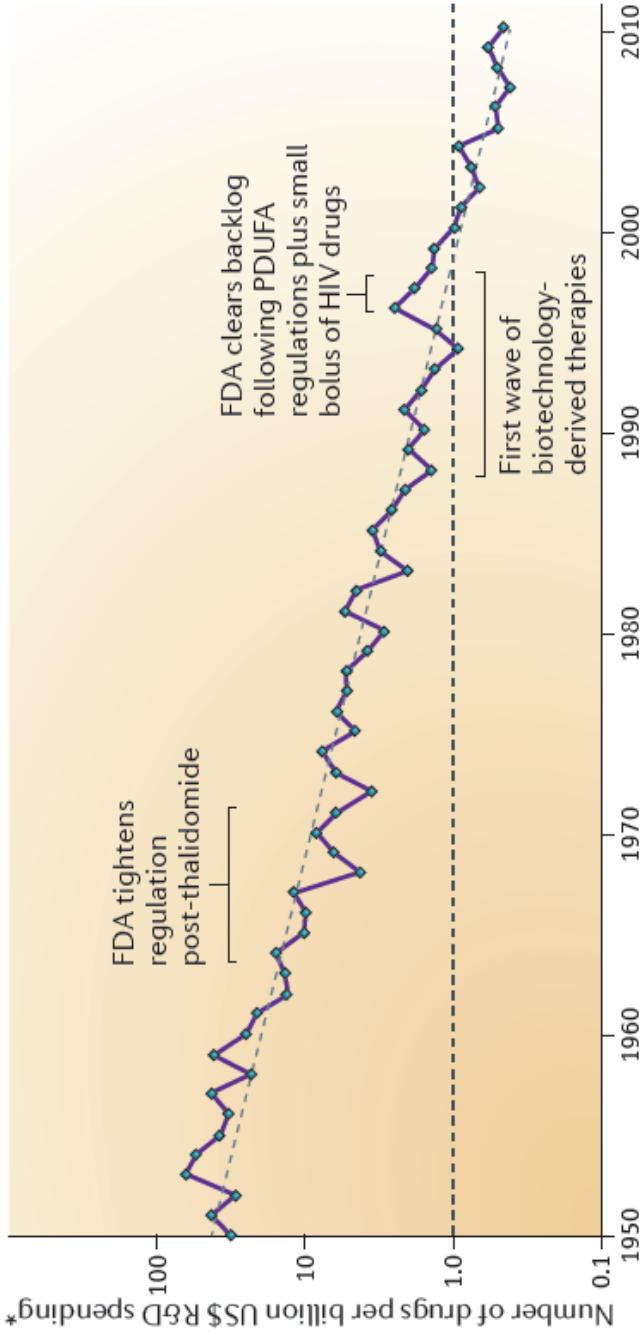

FIGURE 2 Overall trend in R&D efficiency (*inflation-adjusted).
NOTE: The research and development costs are based on the Pharmaceutical Research and Manufacturers of America Annual Survey 2011.
SOURCES: Austin presentation, July 24, 2019; Scannell et al., 2012.

This law observes that "the number of new drugs approved per billion United States dollars spent on research and development has halved roughly every 9 years since 1950" (Scannell et al., 2012, p. 191). It is difficult for any type of industry to survive decades of negative productivity growth, Austin said. Companies might merge or go out of business, and the cost of their products could be "exorbitantly expensive." Understanding a disease does not necessarily lead to an effective treatment and developing a treatment does not necessarily mean that all those who need it will ultimately obtain or benefit from it.

There is a "tremendous amount of attrition" in the drug development process, Austin said. Current estimates are that the 10- to 15-year discovery and development cycle that results in one new FDA-approved drug costs more than $2 billion, including costs of capital expenditures (DiMasi et al., 2016). This estimate takes into account the fact that about 90 percent of products in development fail.[8] At each stage of the development process starting with basic research, the unit cost per project increases logarithmically (see Figure 3). This means that by the time a late-stage clinical trial is under way the cost could be in the hundreds of millions of dollars. Data published in 2010 by Eli Lilly and Company indicate a cumulative success rate, from target identification to product launch, of 4 percent (Paul et al., 2010). Total out-of-pocket cost for one therapeutic product launch was determined to be $873 million ($1.8 billion capitalized). During the discussion, David Mitchell of Patients for Affordable Drugs asked whether Eroom's Law considers actual R&D costs or reported costs, which he noted can include costs for acquisitions of smaller companies that are based on perceived future value. Austin noted that an analysis by Scannell and colleagues covers 1950 through 2010, and that such acquisitions were infrequent until the 1990s (Scannell et al., 2012).

Translation necessitates making some difficult choices, he continued. For example, for the cost of 1 discovery project, 10 postdoctoral fellows could instead be funded to conduct fundamental basic research, noted Austin. The cost of an inexpensive clinical trial could cover the costs of employing 100 postdocs. This is the current landscape for translational science, Austin acknowledged, noting that this is not where we want to be

[8] Estimates vary widely on how much it costs to develop a new drug according to the analytical approach and the data sources used in the analysis. This is discussed in *Making Medicines Affordable: A National Imperative* (NASEM, 2018).

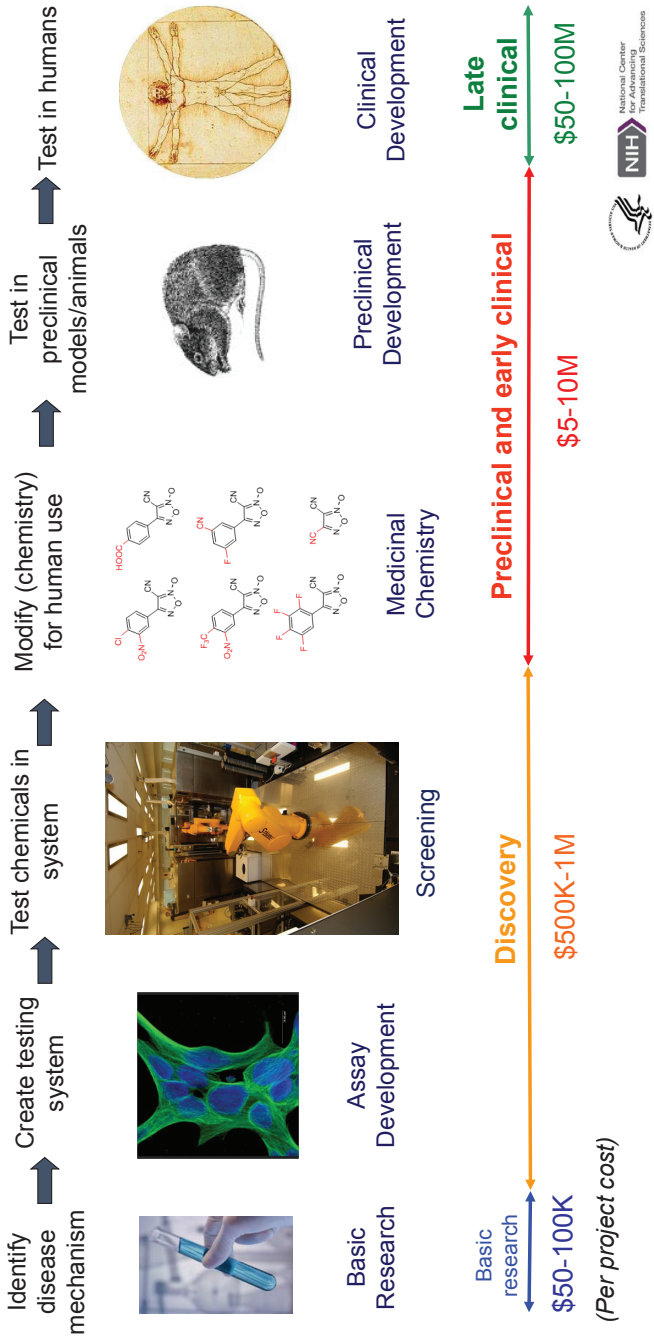

FIGURE 3 Costs increase as translation proceeds (using small molecule drugs as an example).
SOURCE: Austin presentation, July 24, 2019.

and said we have a "societal imperative, scientific imperative, and medical imperative to change this."

Translational Science: Increasing Efficiency, Decreasing Failure

Innovation in translation is key to increasing efficiency and decreasing failure, Austin said. NCATS was established at NIH in 2011 to support innovative new methods and technologies for developing therapeutics faster and more efficiently. It is important to note that NCATS's focus is to establish the science of translation by understanding the scientific and operational principles underlying each step of the translational process. The mission is to transform translational research to be more efficient and effective.

Austin listed examples of areas in translational science where NCATS is working to address problems. These included predictive toxicology, predictive efficacy, reduction of risks in therapeutic development, data interoperability, biomarker qualification, clinical trial networks, patient recruitment, electronic health records (EHRs) for research, harmonized institutional review boards (IRBs), clinical diagnostic criteria, clinical outcome criteria, adaptive clinical trial designs, shortened intervention adoption times, adherence to a therapeutic regimen, and methods to better measure health impact. He stressed that the inclusion of these scientific areas into the translational research landscape would lead to increased efficacy and decreased failure rates.

In addition to scientific issues, there are organizational and cultural challenges—the operational issues—that affect translation. NCATS is working to address issues such as data transparency, intellectual property processes, project management, how to incentivize and award credit for team science and health improvements, education and training, and collaborative structures (e.g., public–private partnerships). NCATS has a variety of programs to help foster advances in translational science, and Austin shared several examples:

- **Clinical and Translational Science Awards (CTSA) Program.** This supports translational science projects and training across a nationwide collaborative network of about 60 academic medical institutions (called "hubs"). The program aims to establish an academic discipline of translational science.[9]

[9] See https://ncats.nih.gov/ctsa (accessed September 23, 2019).

- **Trial Innovation Network.** This is a CTSA initiative that includes Trial Innovation Centers, CTSA Program hubs, and the Recruitment Innovation Center (see below). The network serves as "a national laboratory to study, understand, and innovate on the science and operations of clinical trials."[10] Innovations are needed to improve the flexibility, speed, efficiency, and quality of clinical studies while reducing overall costs, Austin explained.
- **Streamlined, Multisite, Accelerated Resources for Trials IRB Reliance Agreement.** Another CTSA initiative is the Streamlined, Multisite, Accelerated Resources for Trials IRB Platform.[11] Austin noted that as of July 2019, 601 institutions thus far have signed a "reliance agreement" to allow for a single IRB review that will be accepted by all sites in a given multisite trial.
- **Master Contracts.** NCATS is also working to implement a harmonized contracting process for the CTSA hubs.[12] Austin noted that contract negotiations can delay the start of a clinical study for years (Kiriakis et al., 2013). The Trial Innovation Network is currently studying the master contract to assess if contracting delays are reduced.
- **Recruitment Innovation Center.** Very few patients take part in clinical trials, and more than half of NIH-funded trials are unable to meet original goals, Austin said. The CTSA-funded Recruitment Innovation Center at Vanderbilt University is studying innovative approaches to engage patients, especially those from underrepresented populations.[13]

It is possible to decrease cost and increase efficiency for clinical trials, Austin said, but it requires new and innovative approaches. During the discussion, Amitabh Chandra, the Ethel Zimmerman Wiener Professor of Public Policy at the Harvard Kennedy School and the Henry and Allison McCance Professor of Business Administration at the Harvard Business School, added that there is also a need to study why some people become resistant to a drug that had previously worked. Austin agreed and noted

[10] See https://ncats.nih.gov/ctsa/projects/network (accessed September 23, 2019).

[11] See https://smartirb.org (accessed September 23, 2019).

[12] See https://www.ara4us.org (accessed September 23, 2019).

[13] See https://trialinnovationnetwork.org/recruitment-innovation-center (accessed September 23, 2019).

that NCATS has a program that studies individual variation in response to existing drugs. The National Institute of Allergy and Infectious Diseases (NIAID) and the National Cancer Institute also study this topic, in addition to repurposing existing drugs for new indications, he added.

A participant also noted the importance of preventative measures in improving health outcomes and controlling costs and asked about NIH efforts to identify risk for disease and then prevent or delay the onset. Austin referred him to the All of Us Research Program, part of the Precision Medicine Initiative. The program is recruiting 1 million or more people from across the United States to share their health data and contribute biosamples over the long term. The goal is to improve health outcomes through a better understanding of individual differences. Another participant pointed out the recent developments in treatments for HIV and hepatitis C virus (HCV) have reduced the mortality rates for these diseases and asked what might be learned from these successes. Austin responded that there was an investment in understanding the basic virology of HIV and the hepatitis viruses, which allowed for identification of potential drug targets. In addition, particularly for HIV, rapid success could be partially attributed to the collaboration among pharmaceutical companies, which was unusual at the time. He suggested that this success led to other collaborations, both within industry and between the public and private sectors, to advance drug therapeutic development. As an example, he cited the Accelerating Medicines Partnership between NIH and several pharmaceutical companies to find new treatments for lupus, rheumatoid arthritis, type 2 diabetes, and Alzheimer's disease.

NCATS Rare Disease Research Programs

Challenges in translation are magnified when studying rare diseases. There are currently about 7,000 conditions classified as rare,[14] and about 250 new rare diseases are discovered each year (Dawkins et al., 2018). About 80 percent of rare diseases are genetic, and more than half are present in childhood. Austin said that while these conditions are individually rare, they are collectively common, affecting about 8 percent of the U.S. population. Getting an accurate diagnosis for these conditions can take 5–15 years. FDA-approved treatments are available for only about 5 percent of rare diseases, and costs of care and loss of productivity can be exorbitant. He

[14] Defined in the United States as a disease affecting less than 200,000 people.

estimated that, at the current rate of innovation, it would take 2,000 years to develop treatments for all known rare diseases.

To address this, NCATS is taking a "many diseases at a time" approach to research, Austin explained, by identifying commonalities and developing common platforms for diagnosis and treatment. Programs include the Genetic and Rare Diseases Information Center for patients; the Rare Diseases Registry Program, developing interoperable registries; a toolkit to empower patients as research partners; the Rare Diseases Clinical Research Network, conducting national history and interventional studies; the Therapeutics for Rare and Neglected Diseases program, supporting preclinical development; and the development of gene therapy platforms to reduce time and cost of therapeutic development.

Models for Drug Discovery

Even after years of preclinical development, 90 percent of drugs that enter clinical trials in humans are never approved, Austin said. In the majority of cases, this is because of a lack of efficacy or safety (Arrowsmith and Miller, 2013), which is often due to the lack of concordance between the animal models of efficacy or toxicity and actual human experience.

NCATS is looking to address this problem by developing new models for drug discovery. Austin mentioned examples of human cell models, including iPSC technology, spheroids, and organoids. For example, 3-D tissue bioprinting has been used for retinal tissue, blood vessel wall, and skin. Tissue chips are microphysiological systems that model the structure and function of human organs for safety and efficacy screening. About the size of a microscope slide, this platform combines stem cell, tissue printing, microfluidic, cell sensor, imaging, and computing technologies. Chips can be made with normal iPSCs or designed to model physiology and disease by using iPSCs derived from the cells of patients with a particular disease. Austin noted that the tissue chip program is a collaborative initiative involving NCATS and other NIH institutes, centers, and offices; FDA; the Defense Advanced Research Projects Agency; the International Consortium for Innovation & Quality in Pharmaceutical Development; and pharmaceutical companies.[15]

[15] See https://iqconsortium.org (accessed September 23, 2019).

Moving Forward

To facilitate discussion, Austin referred participants to the President's Management Agenda.[16] He commented on Goal 14, which is to "improve transfer of federally funded technologies from lab to market." He highlighted several of the strategies for Priority #14, including increasing entrepreneurship, increasing public–private collaborations, and increasing the efficiency of technology transfer from NIH to private-sector developers.

Austin also reminded participants of the history of a "reasonable pricing clause" that was added to licensing agreements for NIH inventions in the late 1980s, including inventions arising from cooperative research and development agreements (CRADAs).[17] He said that, "if the CRADA resulted in an invention, and the participating company chose to take an exclusive license to that invention, the company would be required to reasonably price the commercialized drug that resulted from the invention." Following public hearings held by NIH in 1994, it was decided that the clause "was driving industry away from collaborations, resulting in fewer opportunities to advance research and promising treatments," so NIH removed the clause from CRADAs and exclusive license agreements. He noted that the number of NIH-industry CRADAs subsequently tripled. During the discussion, John Thomas from Georgetown University pointed out that there is much debate about correlation and causation relative to the removal of the reasonable pricing clause and an increase in the number of CRADAs.

In closing, Austin emphasized that translation requires a team effort with a wide range of different expertise and collaborative work to achieve a common goal that none could achieve alone. The idea of a "lone scientist" making a critical discovery in the laboratory is exciting and is a model that can work well in basic research; however, for translational science to be successful, a team-based approach is essential. "Innovation, partnership, and mutual recognition of the complementary contributions of many team members and different organizations are absolutely required to advance science and medicine to benefit millions of patients who are in need and who need us to succeed," he concluded.

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[16] See https://www.performance.gov/PMA/Presidents_Management_Agenda.pdf (accessed September 23, 2019).

[17] CRADAs provide an opportunity for NIH investigators to join with individuals from industry and academia in the joint pursuit of common research goals.

FEDERAL BIOMEDICAL RESEARCH FUNDING AND NEW DRUG DEVELOPMENT[18]

The first panel of the workshop considered the impacts of publicly funded biomedical research on drug development, particularly how investments by NIH that contribute to the development of drugs that reach the market could be better tracked, quantified, and documented. The session was moderated by Amitabh Chandra, the Ethel Zimmerman Wiener Professor of Public Policy at the Harvard Kennedy School and the Henry and Allison McCance Professor of Business Administration at the Harvard Business School.

Perspectives on the Federal Role in Advancing Drug Development Innovation

"A central objective of biomedical research is learning how to prevent, diagnose, treat, and cure human disease," said Janet Woodcock, director of the Center for Drug Evaluation and Research at FDA. NIH has been committed to conducting and supporting biomedical research since its founding, with a focus on understanding fundamental biological processes including how molecular interactions impact physiology. Woodcock described basic discoveries as "the substrate" for biomedical product discovery and development by pharmaceutical and medical device companies. These companies take the newly discovered potential targets identified by basic science, screen for potentially active compounds, and then selectively narrow the field down to a small number of potentially viable product candidates. After targets and product candidates have been identified, adequate preclinical evaluation of safety and pharmacology is required before FDA will allow their testing in humans. Once something is designated as an investigational new product (drug, biologic, device), human studies can begin to evaluate its balance of benefits and harms for potential market approval.

With regard to Eroom's Law, Woodcock said that the number of new molecular entities (i.e., new drugs, not derivatives of existing products) approved each year by FDA has been steady for decades, except for the past few years. Although the pharmaceutical industry has grown substantially

[18] Throughout this summary, the terms "federally funded," "publicly funded," or "NIH-funded" research refer to both extramural research supported by government grants and intramural research conducted in NIH or other government laboratories.

and invested heavily in development, productivity as measured by approved drugs has been relatively stable. Woodcock added that products that do achieve regulatory approval to market are not guaranteed market success. "The cost of all of these failures weighs heavily on the few successes that actually make it onto the market to recoup the cost of running this entire process," she summarized.

To date, translation has been left to the industry, Woodcock said. Knowledge gained by each company in the course of product development is considered an asset and generally not shared, thus limiting the ability to advance translational science. NIH is focused on generating foundational biomedical science knowledge, including new knowledge that helps to advance product development. NIH is a source of technical and disease expertise for FDA and has a significant role in training the next generation of scientists who go on to work in industry, academia, and FDA, she added. Although NIH understands and contributes to the science of how to evaluate various therapeutic candidates, it does not have the expertise to develop individual products, Woodcock said, adding that "the NIH enterprise is necessary" for the advancement of product development, but "it is not sufficient." NIH does have the expertise and ability to conduct and fund translational science, and she said that translational science "needs to be recognized as a critical scientific link in the chain." Translational science can provide the opportunity to lower the cost of biomedical product development and improve patient access, she said.

Embracing Translational Science at NIH

The essential missing element in the drug development process, Woodcock said, is the knowledge and ability to "pick the winners" and reduce the failure rate of products that enter clinical development. She said that NIH has not yet fully embraced translational science, despite the efforts of NCATS. She concurred with Austin that translational science is team science. Translational science is also expensive, often requiring studies in humans (e.g., the qualification of biomarkers).

Embracing Translational Science in Academia

Translational science has not been considered a prestigious or academic activity, Woodcock continued, yet it is essential to advance the development of biomarkers, outcomes measures, and clinical trial techniques platforms

that can decrease cost and time (e.g., Bayesian methodologies and adaptive trial designs). Woodcock observed that academic scientists and clinicians are interested in translational science, but funding is limited, and this research is not rewarded by evaluation and promotion systems.

Austin agreed that the academic environment into which NIH translational science trainees emerge is not conducive to professional promotion and tenure. As a result, many of these trainees pursue careers at pharmaceutical or biotechnology companies and are lost to NIH tracking. He noted that the NCATS intramural program is team-based, there are no principal investigators (PIs), and every project is a collaboration. This approach has been highly productive, he added, but is only possible because NCATS is not part of a university. He reiterated that NCATS is working to establish translational science as an academic discipline. These departments of translational medicine will have different promotion, tenure, and publishing structures, he said, and would therefore likely need to operate under a separate funding mechanism and scientific review group (i.e., study section).

Ashley Stevens, president of Focus IP Group, LLC, also agreed that translational science at universities is underfunded. The government's primary investment in external translational science is through the Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) programs, which support small businesses to which university technology has already been transferred. He recommended a new translational science funding program, perhaps through the National Institute of Standards and Technology (NIST), to support the early translation steps that take place at universities. He also cited the Wallace H. Coulter Foundation's Translational Research Partnerships as a successful philanthropic model.[19]

Other Avenues for Government to Improve the Success of Product Development

Margaret Blume-Kohout, assistant professor of economics at Gettysburg College, observed that doubling the NIH budget led to an increase in the number of biomedical doctoral degrees awarded. However, she suggested that it is the number of staff science jobs that need to be scaled up, not the number of PIs. Tanisha Carino, executive director of FasterCures, suggested

[19] See http://whcf.org/coulter-foundation-programs/translational-research/coulter-translational-partnership-tp-and-research-awards-ctra (accessed September 23, 2019).

that another role for the government could be to facilitate patient enrollment in clinical trials, including making clinical trial information easier to navigate and understand. She noted that half of Phase 3[20] clinical trial terminations are due to failure to achieve adequate enrollment.

Given the dearth of translational science in academia, Chandra asked whether NIH intramural research should include more translational science, with more attention to the areas mentioned by Woodcock that would advance activities related to regulatory approval. Woodcock suggested that the focus should really be on making the entire drug development process more efficient and cost-effective for patients. She said that drug development needs to be more similar to "engineering" and less "trial and error" every time. One way to improve patient outcomes is through platform trials, she suggested. For example, rather than individual trials asking specific questions about specific interventions, there could be disease-focused trials, studying different interventions to achieve continuous disease improvement over time. A platform approach would reduce start-up costs, she explained, as the trial is ongoing in different subsets of patients and control groups, and new interventions can be incorporated as they become available.

Accounting for Public Funding in Drug Pricing

It is important to recognize that early-stage basic biomedical research is generally a high-risk investment, and it is public funding that takes on this risk and supports these endeavors, said Aaron Kesselheim, professor of medicine at Brigham and Women's Hospital/Harvard Medical School. Private investment in early-stage research is less common. A dilemma from the policy perspective is that in the United States, "the entity that controls the intellectual property on these products can charge what the market will bear." Breakthrough medicines are often marketed at prices that are unaffordable for patients, potentially leading to dire personal financial and health outcomes. This approach to drug pricing is unsustainable and unfair to the public, whose taxes fund much of this research, he said.

[20] Large-scale clinical trial in which the safety and the efficacy of an intervention are assessed in a large number of patients. FDA generally requires new drugs to be tested in Phase 3 trials before they can be put on the market.

Developing "Truly" Transformative Drugs

Kesselheim and colleagues studied the development pathways of the "most transformative" drugs across 12 different medical specialties in a 25-year period (1984–2009), as identified by a survey of U.S. physicians (Kesselheim et al., 2015). The development history of each product was assembled from primary sources (e.g., original research articles, patents) and interviews. He reported that, prior to Phase 2[21] of clinical development, the research behind many of these drugs was done at academic medical centers or government laboratories, often with public funding. In some cases, this early work was also "aided by industry collaborators." After an investigational product entered Phase 2 clinical trials, he said, the primary work had shifted to a pharmaceutical manufacturer, with academic researchers and industry scientists "closely involved in the development."

As shown by the study, a common role fulfilled by academic scientists was interpreting their basic research to conceptualize a therapeutic approach, and in some cases, conducting studies to demonstrate proof of concept. Examples mentioned by Kesselheim included epoetin (Epogen) and imatinib (Gleevec). He continued that in some cases, the "seminal scientific concepts" were conceived by academic researchers and followed up in industry, as happened with the development of fluoxetine (Prozac). There are many more current examples of the significant contribution that publicly funded research makes to the discovery and development of transformative drugs, and Kesselheim mentioned chimeric antigen receptor T-cell (CAR-T) therapies, treatments for HCV infection, and emerging gene therapies. He concluded that the "substantial public investment in drug discovery leads to many of the most transformative drugs."

Direct and Indirect Effects of Public-Sector Funding on Drug Development

To inform the discussion of the role of NIH in drug development, Bhaven Sampat, associate professor at Columbia University and research associate at the National Bureau of Economic Research, described his research on the direct and indirect effects of government support. A *direct effect* of public-sector funding would be a public-sector research institute

[21] Clinical trial in which the safety and preliminary efficacy of an intervention are assessed in patients.

(e.g., NIH or an NIH grantee) discovering and patenting a compound. *Indirect or enabling effects* of public-sector support could include key insights emerging from public-sector research (e.g., new knowledge about disease mechanisms and how they might be interrupted), or the public sector developing research tools, techniques, and instruments. Sampat noted that there are other potential public-sector roles that were not part of his analysis, such as tax credits or involvement in clinical trials, training of scientists, procurement, or partnerships.

It is important to understand and distinguish between the direct and indirect roles of the public sector when discussing policy, Sampat said. Both direct and indirect effects are relevant when evaluating returns on NIH investments, for example. Direct and indirect public-sector contributions are also relevant in discussions of drug prices and patent exclusivity as they relate to private-sector research costs. Only direct effects (e.g., the ownership of patents) would be relevant in discussions of the public-sector role in downstream prices and access.

Sampat set out to measure these direct and indirect effects of public-sector funding using patent information, publications associated with NIH grants, and other publicly available data (Sampat and Lichtenberg, 2011). Out of the 478 new molecular entities approved by FDA from 1988 through 2005, 379 were associated with at least one patent. In 9 percent of cases, it was a public-sector patent, classified as a direct effect of public-sector funding. In 48 percent of cases, a public-sector patent or publication was cited, and these were classified as indirect. When considering only drugs granted priority review by FDA, 17 percent were deemed direct and 65 percent indirect.

There are limitations to this approach. For example, when measuring direct effect, government interest is not always reported by grantees, statements in patents are often incomplete, or information may be missed because it is in continuations or certificates of correction filed later (Rai and Sampat, 2012). To enhance robustness, Sampat looked across all academic or public-sector assignees (instead of government interest statements) and found that the direct effect increased to 13 percent overall and to 22 percent for priority review drugs. Limitations to measuring indirect effects stem from the fact that patent citations are included in drug patents for specific legal and strategic purposes; they are not necessarily indicative of "intellectual influence or knowledge flows," Sampat said. There is also the challenge of measuring indirect effect when a drug patent application cites public, private, and unfunded research.

Kesselheim observed that there are critical elements of the drug development process that stem from NIH-funded research (e.g., certain biomarkers, cell lines, vectors) that might not be quantified because they are often not reflected in drug patents. Sampat agreed that these contributions are often missed in analyses of indirect effects. Because there are generally multiple patents associated with an approved drug, Chandra noted the need to also determine the relative importance of each patent to the development of a product. Sampat agreed and suggested that the extent to which the patent for the active ingredient of the drug is associated with public-sector funding is important to determine. Tahir Amin, co-founder and director of Initiative for Medicines, Access, & Knowledge, Inc. (I-MAK), suggested looking back to see if any of the patents linked to an NIH grant were subsequently revoked or challenged.

Sampat and colleagues are currently updating their analysis with data through 2017, and shared a preliminary assessment that shows similar trends to the original analysis in that both the direct and indirect effects are more evident for priority review and first-in-class drugs. The effect of public funding is largest for the top 20 drugs by United States sales in 2018, at 35 percent for direct effect and 90 percent for indirect. Sampat pointed out that, even though the overall percentages of drugs where there is a direct or indirect effect increased, the relative contributions of direct versus indirect effects are similar across analyses.

Implications and Policy Considerations

The majority of priority review, first-in-class, or top-selling drugs (70–90 percent) can be classified bibliometrically (i.e., by citations) as indirectly linked to publicly funded research, Sampat summarized. Questions for further analysis include whether the cited NIH publication is pivotal, its relative importance compared to the other publications cited, and whether intellectual contributions are captured by the citation.

Sampat said that, across the different studies presented (covering different drugs and time spans), the analysis suggests that about 10 percent of all drugs and about 20–30 percent of priority review, first-in-class, or top-selling drugs can be directly linked to publicly funded research. Questions for further analysis include whether 20–30 percent would be considered a large or small amount; whether it is feasible for government to leverage this direct role by influencing product price and patient access, and, if so,

whether it should; and whether the government should play more of a direct role in later-stage drug development.

Gauging the Returns on Federally Funded Basic Research

Sampat described a method that traced back from new drugs, through publications and patents, to publicly funded research. In contrast, Danielle Li, associate professor at the Massachusetts Institute of Technology Sloan School of Management and a faculty research fellow at the National Bureau of Economic Research, described a method that traces forward from NIH grants, to associated publications, to patents and products (Azoulay et al., 2019; Li et al., 2017). Li said that to fully assess the value of public funding, it is also necessary to try to understand what would happen to product development in the absence of publicly funded research (if NIH did not exist).

There is evidence of spillovers of NIH funding to private-sector firms, Li said. On average, she summarized, about one-third of NIH grants result in research that is cited by a private-sector patent. She noted as a caveat that not all patents lead to drugs. Li described an initial sample of about 150,000 grants funded by NIH from 1980–2005, of which about 66,000, or 43 percent, led to research that was cited by more than 83,000 unique private-sector patents. This translates to "about 36 percent of the total life science patents issued from 1980 through 2012," she continued. Li noted that the grants in this sample originated across NIH, spanning 17 institutes and centers and 548 study sections.

Li shared data showing that NIH-linked private patents did vary somewhat by disease area, which she clarified is not indicative of the effectiveness or lack thereof of a given NIH institute. It was also observed that funding from one disease area affected patents awarded in other disease areas just as frequently. She said that basic science supported by NIH was cited as frequently as applied science in private-sector patents. Over the study period, the lag time from grant to private-sector patent associated with that grant has decreased, but Li noted that this could have multiple causes, such as NIH grants being awarded further downstream (e.g., for translational science).

Li also concluded from her research that "fewer drugs would be developed in the absence of NIH funding." The first step in estimating the impact of increases or decreases to the NIH budget is to understand the ramifications of bibliometric history as a methodology. An advantage of using citation-linked patents as a measure is that it "traces knowledge flows

explicitly," Li said. In addition, it is possible to trace impact regardless of any disease area discrepancy between grant and patent or time lag from grant to patent award. But there are also limitations, Li continued. The method could result in an underestimate because it looks for publications cited by a patent that specifically list NIH funding. In addition, it does not take into account that many patents in industry are the work of employees who were supported by NIH training grants as students or fellows. Li pointed out that NIH training scientists has a potentially "huge" impact on private-sector development. It is also possible to overestimate the contribution of NIH funding as a result of a "crowding out" effect. In other words, increased NIH funding leads to increased NIH research; then is more research to cite and likely more patents that cite it. While this confirms "that NIH-funded research is commercially relevant," Li said, "it does not necessarily say that NIH funding leads to more innovation." It is possible, she said, that the particular research would have been done regardless.

For this analysis, Li considered all patents associated with a given research area, regardless of whether the patents cited NIH funding. In other words, "does NIH funding in an area increase the total amount of innovation in that area." To accomplish this, Li used Medline Subject Headings (MeSH) terms to identify relatedness between the research area funded by a given NIH institute and the publications cited by a private-sector patent. She noted that she controlled for confounding factors.

Her analysis suggests that $10 million in NIH funding can be causally associated with a net increase of 2.3 patents. Financially, $10 million in NIH funding generates about $3.5–$28 million in present discounted value of drug sales (i.e., value to the manufacturer, not the consumer). Furthermore, $10 million in NIH funding leads to 0.034 more patents associated with FDA-approved drugs, which Li acknowledged might seem small, but it translates to $14.7 million in sales. These and other estimates of financial returns associated with NIH funding suggest that "NIH funding pays for itself using drug sales alone," Li said. The returns on publicly funded research are high even before taking into account the impacts of medical devices, training of scientists, public health education leading to behavior change (e.g., handwashing, smoking cessation, blood pressure monitoring), social value returns (i.e., the value consumers place on the utility of a product), or other approaches to link NIH funding to drugs.

Li cautioned that reaping these returns requires patience, as the lag between funding and impact can be 5–15 years or longer. In addition, it is difficult to direct funding toward a specific outcome.

Quantifying the Impact of Targeted, Disease-Specific NIH Extramural Funding

Margaret Blume-Kohout, assistant professor of economics at Gettysburg College, provided another approach for analyzing the impact of NIH funding. NIH-funded research generates a base of information and a cadre of trained scientists, which could theoretically "serve as a cost-reducing subsidy for biopharmaceutical firms," Blume-Kohout said. Several studies using patent-related endpoints, including those discussed by Sampat and Li, have provided descriptive evidence for a link between public funding and drug development, Blume-Kohout said. The challenge is to determine if there is a causal linkage and to quantify the extent to which drug development actually leads to new drugs, and the extent to which those drugs improve quality of life for end users. Blume-Kohout concurred with Li about the need to understand "what NIH is doing that would not otherwise be done and the potential for crowding out."

In other research, Blume-Kohout described her method of assessing the impact of targeted, disease-specific NIH extramural research funding on the development of treatments for that disease (Blume-Kohout, 2012). To start, she classified NIH extramural research grant awards from 1975 through 2006 by disease. She developed a classification algorithm using MeSH terms, synonyms, and hyponyms to overcome the drawbacks of Boolean keyword searches. She explained that Boolean searching by keyword can be problematic because multiple different words may be used to describe the same disease condition and, in some cases, grant abstracts may not mention the related disease or condition explicitly. For example, a grant for malaria research might not include "malaria" but rather list an associated pathogen (e.g., *Plasmodium*), vector (e.g., *Anopheles* mosquito), alternative name (e.g., Marsh Fever), treatments, or even symptoms or signature cellular characteristics. While an expert reading a grant would know it was about malaria, she continued, keyword searching could miss many related grants.

Employing an econometric model, Blume-Kohout estimated that "a sustained 10 percent increase in targeted, disease-specific NIH funding yields approximately a 4.5 percent increase in the number of related drugs entering clinical testing (Phase 1 trials), after a lag of up to 12 years" (Blume-Kohout, 2012). She observed that this estimate is consistent with the findings of studies on the impact on NIH funding on pharmaceutical innovation that measured patents and research expenditures. There was, however, no evidence of any impact on the initiation of Phase 3 clinical

trials. According to Blume-Kohout, these results "should not be interpreted as asserting that all disease-specific public research funding is impotent with respect to pharmaceutical innovation" (Blume-Kohout, 2012, p. 656). Blume-Kohout and Clack found some evidence of partial crowd-out when the number of NIH-funded research assistantships increased but no evidence of crowd-out when the number of NIH-funded traineeships and fellowships increased (Blume-Kohout and Clack, 2013). As a caveat, she noted that the analysis considered only traditional, investigator-initiated extramural research project grants and did not include clinical research centers, translational science via SBIR or STTR mechanisms, traineeship programs, or intramural funding. Importantly, she said, the econometric model estimated the effects of *changes* in the levels of NIH funding across diseases, not the "total number of drugs and the extent to which NIH contributes to that total." She also cautioned that this approach, which she said evaluates disease-specific funding as a "policy lever," ignores the serendipitous or spillover effects of NIH funding discussed by Li.

To illustrate the roles of NIH funding in the development of a marketed drug, Blume-Kohout gave a brief overview of the development pathway of the cancer drug Istodax (romidepsin). In summary, she said that NIH had a role in supporting the fundamental science, publications, training of researchers, clinical trials, intramural research, and cooperative agreements with public and private partners.

Future Directions

Blume-Kohout highlighted several areas for future research. She suggested that machine learning and statistical text analysis could be used to better elucidate the role of NIH in "the genesis and evolution of ideas" and to help classify publications relative to quality or importance. There is also a need to better follow the careers of students who are supported directly or indirectly by NIH funding, she continued, and understand the extent to which they pursue careers in drug development or industry. These data are often restricted access, she noted. Finally, it is also important to evaluate different funding mechanisms, such as the SBIR and STTR programs, for their effectiveness in supporting "useful innovation," she said. Special attention should also be given to understanding the influence of translational science and collaborative research mechanisms.

Improving Data Resources

Ameet Sarpatwari, instructor in medicine at Harvard Medical School and assistant director of the Program on Regulation, Therapeutics, and Law at Brigham and Women's Hospital, asked how current use of data resources for these analyses (e.g., ClinicalTrials.gov, NIH RePORTER) might be augmented, or what new databases might be created, to better develop the evidence base for quantifying the contribution of NIH to drug development. Li responded that it would be helpful to have more information on spending. For example, there is often restricted access to further details about how grantees are selected, such as the individual reviewer scores. Once funding is granted, how does NIH ensure that it will have impact (e.g., are there incentives or conditions associated with the grant)? She also noted that it would be helpful to have access to drug price data, including rebates, and some method of measuring the clinical value added for a given drug. She added that there is also the challenge of determining causality, and it would be helpful if changes to how grants are awarded could be structured in a way that facilitated evaluation relative to other approaches. Sampat said it would be useful to have "anonymized information about licensing of intramural and extramural inventions." Ideally, it would also be helpful to have access to data on the cost of publicly funded clinical trials for drugs, although he acknowledged there are challenges to sharing this type of data. Sampat added that it could be helpful to have an equivalent of the FDA Orange Book for biologics.[22] Thomas referred participants to the FDA Purple Book,[23] which lists licensed biological products.

Reforming the Patent System

The patent and copyright clause of the U.S. Constitution (U.S. Const. Article I, Section 8) gives Congress the power "to promote the progress of science and useful arts, by securing for limited times to authors and inventors the exclusive right to their respective writings and discoveries." Tahir Amin of I-MAK emphasized the phrase "limited times" and said that pat-

[22] The Orange Book is the common name for the FDA publication *Approved Drug Products with Therapeutic Equivalence Evaluations*.

[23] The Purple Book is the common name for the FDA publication *Lists and Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations*, which lists innovator biological products and any biosimilar and interchangeable biological products licensed by FDA under the Public Health Service Act.

ent protection provides an initial benefit to society, but the longer patent exclusivity extends, the less society benefits.

There is a variety of tactics that companies use to protect and extend their product monopolies. Companies refer to "life cycle management, incremental improvements, and incremental innovation," Amin said, while those in public health use terms such as "evergreening, strategic patenting, or defensive patenting" to describe the same tactics.[24]

I-MAK analyzed the top 12 selling drugs in the United States (8 biologics, 4 small molecule drugs) and found, on average, 125 patent applications filed and 71 patents awarded per drug. The result is an average of 38 years of attempted protection from competition, Amin said. Since 2012, these drugs have increased in price by an average of 68 percent (with the exception of Herceptin, which decreased by 58 percent).[25] Amin elaborated on AbbVie's Humira as an example. Eighty-nine percent of all patent applications for Humira were filed after it was approved by FDA in 2002, and 49 percent were filed after the first patent expired in 2014. Amin questioned the extent to which this post-approval activity was "innovation" or "inventive." He noted that there are nearly four times more patent applications filed in the United States for Humira than in Europe. One outcome of this is that a biosimilar of Humira was launched in Europe in 2018, but patent litigation in the United States will prevent approved Humira biosimilars from being marketed until 2023. To illustrate the impact of secondary patenting, Amin briefly described the patent pathways of four drugs that benefited from federal funding (see Box 3).

IMPACT OF PATENT AND TECHNOLOGY TRANSFER POLICIES ON NIH-FUNDED INNOVATION

In this session, panelists reviewed the current state of technology transfer agreements and considered models for spurring drug innovation. Moderator Stephen Merrill, senior research fellow and former executive director of the Center for Innovation Policy at Duke Law, reminded participants

[24] Evergreening is a strategy to extend a product's patent exclusivity by filing for additional patents before the original patent expires. This topic is discussed in *Making Medicines Affordable: A National Imperative* (NASEM, 2018).

[25] This decrease in price came in a short period in mid-2017 and only after the drug had increased in price by 15 percent over the past 5 years. The price decline was attributed to a variety of factors, including increased competition from other breast cancer products and a disappointing clinical trial result with a Herceptin combination.

BOX 3
Case Examples of Patenting Federally Funded Drugs

- **Norvir/Kaletra (AbbVie)** The development of Norvir (ritonavir) to treat HIV was supported by a National Institute of Allergy and Infectious Diseases grant, and the original patent is associated with this grant. Norvir was approved in 1996 and later combined with another HIV drug and approved as Kaletra (lopinavir/ritonfavir) in 2000. As of 2012, there were more than 107 patent applications filed by AbbVie for this product. Worldwide sales in 2012 were $1.4 billion. Amin noted that AbbVie continues to file patent applications for this product (Amin and Kesselheim, 2012).
- **Lyrica (Pfizer)** The original patent for Lyrica (pregabalin) was supported by a National Institutes of Health (NIH) grant to Northwestern University. Lyrica was approved in 2004, and annual worldwide sales were $5 billion in 2017. By 2018, more than 118 patent applications had been filed. Amin added that 18 percent of Northwestern University's endowment is income from Lyrica, with $360 million in licensing income reported in 2014. Since 2012, the drug's price has increased 163 percent. Amin pointed out that during the lifetime of the licensing agreement, it was in Northwestern's best financial interest for Pfizer to continue to extend its patent protection.
- **Januvia (Merck)** The original patent for Januvia (sitagliptin) was supported by an NIH grant to the Trustees of Tufts College. Januvia was approved in 2006; as of 2018, 41 patent applications had been filed. In 2018, annual worldwide sales reached $5.9 billion.
- **Truvada (Gilead)** There are four federal government patents associated with Truvada (emtricitabine and tenofovir disoproxil fumarate), with the first awarded in 2007 and the most recent in 2018. Truvada was approved for pre-exposure prophylaxis (PrEP) in 2012. As of 2018, there were at least 72 patent applications filed by Gilead Sciences that relate to Truvada both for treatment of HIV and/or PrEP, and worldwide annual sales in 2018 were $3.1 billion. Amin pointed out that in this case, it is the government that had filed and been awarded secondary patents (the prophylactic use patents).

SOURCE: Amin presentation, July 25, 2019.

that NIH intramural research "is very loosely governed" by the Stevenson-Wydler Act of 1980, which "simply directs federal agencies to develop the capacity to patent and license their inventions." NIH extramural research is governed by the Bayh-Dole Act of 1980, which allows universities, nonprofits, and NIH contractors to assume title to their inventions and to license them to private parties (CRS, 2012, 2016). Merrill noted that some have argued for NIH to exercise its march-in rights under the Bayh-Dole Act.[26] That provision allows government to compel the relicensing of a federally funded invention if the patentee or its licensee has not developed the invention or made it accessible to the public under reasonable terms. He added that the question of what is actually patentable also persists. A series of recent Supreme Court decisions ruled on the patenting of particular biomedical research inventions and computer software developments, Merrill said, and there have been calls for legislation to more clearly define what is patentable.

Panelists elaborated on these issues, discussing:

- the landmark legal cases that have attempted to clarify what is patentable;
- the current state of academic technology transfer;
- the practicalities of exercising march-in authority; and
- how stakeholders view the technology transfer process.

Patent-Eligible Subject Matter in Biomedical Research and Development

Arti Rai, professor of law and faculty director of the Center for Innovation Policy at Duke Law, discussed the uncertainty surrounding what constitutes as patent-eligible subject matter and the implications of this uncertainty for biomedical R&D. She described three Supreme Court cases as representing "the most important substantive patent law change in the last few decades." The cases are *Mayo Collaborative Services v. Prometheus Laboratories* (2012),[27] *Association for Molecular Pathology v. Myriad Genetics*

[26] For detailed information about the Bayh-Dole Act (Public Law 96-517, the Patent and Trademark Act Amendments of 1980) and march-in rights, see 37 CFR Part 401 at https://grants.nih.gov/grants/bayh-dole.htm (accessed September 23, 2019).

[27] 566 U.S. 66 (2012).

(2013),[28] and *Alice Corp. v. CLS Bank* (a software patent case in 2014).[29] This is a very complex topic, Rai acknowledged, as she described the cases.

The *Association for Molecular Pathology v. Myriad Genetics* case involved gene patents related to genetic testing to assess breast cancer risk, and while it received significant public attention, Rai said it was perhaps the least influential, at least with respect to drug patents. The case established a technical distinction between genomic DNA (gDNA) and complementary DNA (cDNA), ruling that gDNA was subject to a "product of nature exception" but allowing the patenting of cDNA molecules (Rai and Cook-Deegan, 2013).

The *Mayo Collaborative Services v. Prometheus Laboratories* case, Rai explained, involved a patent for a method of measuring the metabolite level of a particular drug to determine the need to increase or decrease the dose of the drug. In ruling that the method in the Prometheus patent was unpatentable, the decision upheld and fortified the "law of nature exception" to patent eligibility. The *Mayo* case led to a two-step analysis process for determining patent eligibility, which was explicitly reaffirmed in the *Alice* case, Rai said. At the first step, the test determines if the invention is potentially unpatentable because it is "directed to" a law or product of nature. If the first step raises a concern about unpatentability, the test's second step asks if the invention includes an "inventive step" that goes beyond the law of nature so as to make the invention that would make it patent eligible. The standard is not clear, however, and she noted that congressional hearings were held recently to consider whether legislation is needed. Interestingly, the *Alice* case did not refer to the *Myriad* case, and Rai observed that the recent congressional hearing did not take up the issue of gene patents either.

Whether patents are a suitable measure of innovation depends on what the patent covers, Rai said. There is much debate about the strategy of "evergreening," and what constitutes an innovative precision medicine patent versus an evergreening patent can be very subjective. The Prometheus patent in the *Mayo* case is considered by some to be evergreening, Rai said, because the patent claim was not non-obvious (that is, it was obvious). "That is a problem with the patent," Rai said, "but that is not necessarily a problem with respect to patent-eligible subject matter," and she suggested that the *Mayo* decision was perhaps "overinclusive." The concern, she continued, is

[28] 569 U.S. 576 (2013).
[29] 573 U.S. 208 (2014).

the potential impact of the *Mayo* decision on precision medicine, which is rooted in laws of nature. She added that a recent Federal Circuit opinion concluded that method-of-treatment claims are patentable (*Vanda Pharmaceuticals v. West-Ward Pharmaceuticals*) and that the U.S. Patent and Trademark Office (USPTO) has been granting method-of-treatment patents.

Rai suggested that there are better approaches to reducing evergreening than the *Mayo* decision. She proposed that the Patent Trial and Appeal Board could address evergreening as part of its mission to decide questions of novelty and non-obviousness in patents. John Thomas, professor of law at Georgetown University, suggested that the courts should consider a range of other factors when making patentability decisions, including the pace of innovation, current information-sharing norms, other intellectual property rights, such as trade secrets or regulatory exclusivities, the rate of industry concentration and patterns of enforcement in that industry, and professional incentives for innovation.

Technology Transfer at U.S. Academic Institutions

In 2011, the consensus study report *Managing University Intellectual Property in the Public Interest* included recommendations for improvements to the technology transfer system (NRC, 2011). Stevens briefly showed some of the trends in academic technology transfer, which indicate steady increases across a range of parameters in recent years (e.g., academic invention disclosures, research expenditures, patent applications and awards, legal expenditures, patent expenditures, licensing activity, start-up companies formed, income from licensing). One area Stevens highlighted was license exclusivity. He said that the percentage of nonexclusive licenses has increased steadily in recent years and, correspondingly, the percentage of exclusive licenses has steadily declined. Staff of university technology transfer offices provided one interpretation of this trend; they suggested to Stevens that exclusive licenses are still being secured for drugs and other high-value intellectual property, but there has been a steady increase in the number of licenses for technologies that do not require exclusivity, such as biologics, research tools, or software. Stevens added that another positive change in recent years is an increase in the number of staff with substantial industry experience in university technology transfer offices. This expertise helps universities to better assess the potential value of early-stage technologies.

Stevens presented some statistics on technology transfer in academia and some very recent data on FDA-approved products that can be traced

back to public-sector intellectual property that was transferred to the private sector. He said that universities only file patents on 55 percent of invention disclosures, and top universities only license 52 percent of their new patent filings. He continued that the median time from licensing to disclosure is 4 years, and only 5 percent of new patent filings result in a licensed product. The average income-generating license yields $132,000 per year. In 2017, out of 20,517 income-generating licenses, only 189 (0.9 percent) brought in more than $1 million, Stevens added. He said that these data, as yet unpublished, are an update to Stevens et al. (2011). He summarized that of 357 FDA-approved drugs, biologics, vaccines, and in vivo diagnostics, two-thirds came from U.S. institutions, and NIH was the leading discovering institution. The vast majority were small molecule new chemical entities, particularly in the areas of oncology, infectious disease, metabolic disease, and central nervous system disease.

With rare exceptions, government only funds discovery, not development, Stevens said. To illustrate the cost of development, Stevens reviewed the financial details of the discovery and development of the prostate cancer drug, Xtandi. Briefly, Xtandi was discovered by researchers at the University of California, Los Angeles, and patented in 2005, licensed to Medivation, which subsequently partnered with Astellas. Xtandi was approved in 2012, and Medivation was later acquired by Pfizer. He said that for that level of investment, it is hard to argue for a role of NIH in pricing.

Stevens suggested that quantifying public investment in discovering and validating targets for new drugs is the more relevant statistic and demonstrates a much larger public-sector investment. "The transfer of academic discoveries is making a massive contribution to public health with the discovery of new drugs," Stevens summarized. "The public invests in the discovery of new drugs but very little in the development of new drugs, which is the role of the private sector," he continued. Finally, he stated that "attempts to use the march-in provisions of the Bayh-Dole Act to control drug prices are misplaced and would be highly counter-productive."

March-In Rights

Thomas expanded on the march-in rights authorized under the Bayh-Dole Act. Although the act allows federally funded inventors to patent and license their discoveries, Thomas explained that the government retains a "nonexclusive, nontransferrable, irrevocable, paid-up license" to use the invention for its own benefit. March-in rights, he continued, "allow the

government, in specified circumstances, to require the federal contractor to grant a nonexclusive, partially exclusive, or all-exclusive license to a responsible applicant." The government can act to grant a license directly if the contractor refuses. Although march-in rights actually predate the Bayh-Dole Act, stretching back more than 50 years to President John F. Kennedy's administration, Thomas pointed out that no federal agency has ever exercised its march-in rights.[30] Supporters consider march-in rights to be a potential mechanism for controlling drug prices, Thomas said, while others raise concerns that exercising march-in rights could discourage private investment in the development of early-stage technologies.

March-in rights can be triggered if "the contractor assignee has not taken effective steps to achieve practical application of the subject invention" in the patent [37 CFR 401.14 (j)]. Practical application means to manufacture, practice, or operate "under such conditions as to establish that the invention is being utilized and that its benefits are, to the extent permitted by law or government regulations, "available to the public on reasonable terms" [37 CFR 401.14 (a)]. Thomas emphasized that the statute says "on reasonable terms," and in contract law, price is an element of the terms. It is often said in policy debates, he continued, that "a safe and effective medicine is neither if it is not affordable."

Thomas said that, realistically, patent "march-in rights" are not "a practical, widely available, useful tool" for ensuring affordable drug prices, particularly because these rights do not address other incentives that are available for drug development, such as regulatory exclusivities. In addition, the ability to exercise march-in rights would come fairly late in the process and be subject to appeals before taking effect. But it is also not clear that government exercising march-in rights would actually discourage private investment, Thomas said. He suggested that, given the host of other patent hurdles that companies are prepared to contend with (e.g., invalidation, unenforceability), the prospect of a rare application of "march-in rights" is not likely to be considered a threat to a licensing agreement. Although "march-in rights" are not likely to ever be an effective approach to influencing pricing, Thomas said, "it is a shame" that a 50-year-old authority has never been used and that more oversight is needed in this area.

Stevens pointed out that exercising march-in authority, even once, could fracture trust in the integrity of an academic exclusive license and negatively impact private investment, resulting in many missed opportuni-

[30] See March-In Rights Under the Bayh-Dole Act (CRS, 2016).

ties for product development. He said that the ultimate goal is to translate basic research into products that reach the public and cautioned against policies that would deter the private sector from developing publicly funded research. Rai suggested that the simple threat of using march-in authority can have an impact, and she cited the tensions around stem-cell patenting as an example.

Stakeholder Feedback on the Technology Transfer Process

Chuck Na, an interagency policy specialist at NIST, presented an overview of the recently released report *Return on Investment Initiative for Unleashing American Innovation* (NIST, 2019). The federal government invests $150 billion annually in R&D, Na said, and NIST was charged with facilitating stakeholder dialogue to identify ways to improve the returns on that investment.[31] The NIST ROI [return on investment] Initiative feeds into the Lab-to-Market (L2M) cross-agency priority (CAP) goal, which is among the 14 CAP goals in the President's Management Agenda designed to improve government function.

In conjunction with other agencies, NIST gathered input from technology transfer stakeholders through a Request for Information in the *Federal Register*, a series of public events and other outreach activities. The focus, Na explained, was to identify challenges and collect ideas that could inspire solutions to address technology transfer issues related to federally funded research. Discussions centered on the five key strategy areas of the L2M CAP goal: (1) identify regulatory impediments and administrative improvements in technology transfer policies and practices; (2) develop an entrepreneurial R&D workforce; (3) engage private-sector investors and technology development experts; (4) develop innovative tools to facilitate technology transfer; and (5) understand global trends and benchmarks. The resulting paper describes 15 findings by NIST across the five L2M strategy areas, and Na summarized several findings applicable to the workshop discussions (see Box 4).

[31] NIST is part of the U.S. Department of Commerce and has the authority to promulgate regulations to define and implement the Bayh-Dole Act.

BOX 4
Some Findings from the NIST Report
Return on Investment Initiative for Unleashing American Innovation

Regulatory Challenges

- **March-In Rights.** Stakeholders raised concerns about the lack of clarity for when march-in authority would be used and regarding the definition of "reasonable terms." Although "march-in rights" have never been used, stakeholders suggested that the threat alone has "a cooling effect on the negotiation parts of conversation," Na conveyed.
- **Government-Use License.** Stakeholders felt that the scope of the government-use license in the Bayh-Dole Act is not clearly defined.
- **Preference for U.S. Manufacturing.** Stakeholders sought clarity about the requirement for licensees to manufacture substantially in the United States, and the opportunities for waivers.
- **Copyright of Government Software.** There is a general prohibition on copyrighting government works, and stakeholders reported that this creates "substantial challenges in commercializing software solutions" that have been developed by federal employees who have authored the code.

Engaging the Private Sector

- **Streamlined Partnership Mechanisms.** Stakeholders discussed the range of partnership mechanisms, including cooperative research and development agreement, and noted that there are agency-specific authorities for commercializing technologies that all agencies could benefit from.
- **Technology Commercialization Incentives.** Stakeholders supported programs that help facilitate public–private interactions for technology commercialization activities (e.g., I-Corps).

Entrepreneurial Workforce

- **Technology Entrepreneurship Programs.** Stakeholders discussed with the National Institute of Standards and Technology (NIST) the need for basic researchers to be better equipped to engage with industry.
- **Managing Conflicts of Interest.** Many university stakeholders shared concerns about the need for greater uniformity of agency requirements for managing conflicts of interest.

continued

BOX 4 Continued

Innovative Tools and Services

- **Federal Intellectual Property Data Reporting Systems.** The iEdison database was developed by the National Institutes of Health (NIH) for extramural grantees to report their inventions in compliance with the Bayh-Dole Act regulations. Na reported that stewardship of iEdison will move from NIH to NIST, and NIST will work to create more uniformity in the reporting system. Na said that an interagency workgroup is considering what information should be made available and what consistent practices are needed to ensure that it is accessible.
- **Access to Federal Technologies, Knowledge, and Capabilities.** Stakeholders also sought more access to data across all federal research programs, noting the lack of interoperability across different agency systems.

Understanding Global Trends and Benchmarks

- **Benchmarking and Metrics.** Na reported that initiatives are under way to fully understand the return on investment of federal technology transfer through better benchmarks and metrics.

SOURCE: Na presentation, July 24, 2019.

Interpreting the Bayh-Dole Act

Participants discussed some of the history of the Bayh-Dole Act, including the origins of different provisions, perspectives on which provisions were included to gain the votes for passage, and concerns about awarding license exclusivities. Sampat and Stevens discussed the length of license exclusivities relative to the wide variability in the time it takes to develop and commercialize a product. Stevens emphasized that the pathways from laboratory to marketplace are complex and varied. As an example, he said that the intellectual property for Yervoy, the first checkpoint inhibitor to reach the market, began at the University of California, Berkley, and traversed nine companies over 16 years before becoming an approved product. Stevens highlighted the importance of universities also considering royalty terms in licensing agreements. Furthermore, Thomas noted the availability of FDA-

administered regulatory exclusivities (e.g., new chemical exclusivity, new clinical investigations, pediatric exclusivity).

Participants discussed further how to define when a patent stems from NIH-funded research and when "march-in rights" would apply. Kevin Outterson, professor at the Boston University School of Law and executive director and PI of Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator (CARB-X), noted that while the early research for a new drug may be performed in an NIH-funded university laboratory, the company developing the drug selects a lead candidate, determines the structure–activity relationship, and structurally modifies the molecule for optimal activity before patenting the specific small molecule that will become the investigational drug. He suggested that "march-in rights" might apply to the early work but not to the small molecule patent.

What is "reasonable" and for whom has also been interpreted differently across stakeholders. The NIST interpretation has been that this provision in the Bayh-Dole Act refers to reasonable licensing terms from government contractor to licensee. Na said this interpretation of the legislative intent is based on 2002 testimony by Senators Bayh and Dole. However, Thomas disagreed that "march-in rights" only apply to the terms of the license between the government contract and the licensee. He reiterated that the provision addressing practical application states that the benefits of the invention must be made "available to the public on reasonable terms." Stevens said that the march-in provision was intended to protect universities, which were perceived as "inexperienced licensors" at the time. However, "universities have become very sophisticated licensors," he continued, and he suggested that this is why march-in has not been exercised to address a failure to develop.

Rai and Thomas debated whether "reasonable terms" includes pricing. Rai suggested that the agency has discretion to make a "reasonable interpretation" and cited the "Chevron two-step test."[32] Thomas asserted that "reasonable terms" does include pricing per the "plain meaning"[33] of the statute (step one) and "if there is any ambiguity, this is a reasonable

[32] In *Chevron v. Natural Resources Defense Council* (1984), the Supreme Court established a two-step process to address ambiguity in statues. Step one says, in essence, that if the intent of Congress is clear, the implementing agency must fulfill the intent. Step two says, in essence, if the legislative intent is ambiguous, the courts will defer to the agency's reasonable interpretation.

[33] The "plain meaning rule" says, in essence, that a statute should be interpreted consistent with the ordinary meaning of the language used.

interpretation" (step two). Rai asserted that the statute is ambiguous and the plain meaning is not apparent. She said that if NIST were to decide that reasonable terms included pricing, it could then address the many complex, economic questions that should not be decided by judges.

Expanding on the concept of reasonable terms, Chandra asked how "reasonable price" and "public" are defined. He observed that "a drug could be cost-effective but still completely unaffordable" to many people. Is "the public" the individual, or the payer? He also called out insurance plans for their role in high drug prices (e.g., high deductible health plans, Medicare Part D catastrophic coverage). Thomas suggested it would be instructive to look at the legal discussions about the Fair, Reasonable, and Non-Discriminatory commitments for licensing patents. Fred Ledley, professor at Bentley University, suggested that focusing only on the impact of high prices on access ignores the overall net beneficial impact of licensing on public health, or health care. He also observed that the role of technology transfer goes beyond the creation of a marketed product and includes other benefits, such as job creation.

Standardizing the Licensing Process

A participant observed that university technology transfer policies span a wide range, with some so stringent that they make it difficult for companies to license intellectual property. She asked whether streamlining the process across universities would be beneficial and whether they should perhaps be federally mandated. Na said that individual institutions should be allowed to set their own policies. Public institutions must comply with federal and state laws, while private institutions are accountable to boards and other stakeholders. Na added that NIH has experimented with an express licensing approach for biological materials, which he said involved a nominal fee and a simple letter of agreement that was non-negotiable. Still, he said, there were regular requests for modifications. Additionally, that some universities are not interested in licensing deals and others are very business-friendly "is just the nature of the marketplace," he said.

THE ECONOMICS OF DRUG PRICING

The economic implications of escalating drug prices were the next topic of discussion at the workshop. Patricia Danzon, professor at the Wharton School of the University of Pennsylvania, provided a brief primer on pricing

and reimbursement practices in the United States and panelists representing different stakeholder perspectives shared ideas for innovative business models and financing structures to accelerate drug discovery and development.

Panelists discussed:

- a value-based, cost-effectiveness analysis approach to pricing;
- a "cost-of-cure approach" to funding drug development;
- a "Netflix subscription" model that delinks profit from volume sold; and
- the importance of increasing consumer (i.e., taxpayer) awareness and engagement on pricing issues.

Pricing and Reimbursement of Pharmaceuticals in the United States

While outlining the core economic principles of pricing, Danzon said that, "in any industry, including pharmaceuticals, pricing to capture customers' willingness to pay maximizes profit." When price is set based on cost, she continued, there is no guarantee that the company will cover its costs and break even. Pharmaceutical R&D, like any cost, is related to pricing in that a company takes expected financial returns into consideration when making a decision about whether to invest in a particular project. Once the product is developed and launched, however, any prior research cost is a "sunk cost and is irrelevant to pricing," Danzon explained.[34] Instead, pricing is influenced by the buyer's willingness to pay, which is also referred to as "what the market will bear" and reflects the value to the customer. R&D intensity[35] in the pharmaceutical industry is premised on patenting innovative products, which allows the producer to maintain a monopoly for the patent period, she continued. Per the World Trade Organization, patented inventions are protected for 20 years from filing, which she said was intended to allow the innovator "to recoup sunk research and development costs."

[34] In economics, a sunk cost is a previously incurred expense that cannot be recovered and so should not be taken into account in decision making going forward.

[35] In economics, R&D intensity is a measure of a company's research expenditures relative to sales.

Insurance and Reimbursement in the United States

"Health insurance exacerbates the monopoly effect" on pricing, Danzon said (see Garber et al., 2006). Insurance is intended to shield consumers from high medical costs; because insured consumers only pay a small portion of the price, they are insensitive to the full price. "Unless the payer adopts measures to constrain prices, prices will tend to increase," she said.

In theory, Danzon said, insurance plans should seek to balance financial protection for consumers with access to products and services and control of total costs. To accomplish this, payers develop reimbursement rules that govern prescription product coverage and payment (Danzon et al., 2013). In the United States, she continued, reimbursement rules vary by payer, product, and point of care (e.g., clinic, pharmacy, hospital). Payers do not control the prices that drug manufacturers can charge, and some payers, such as Medicare, are prohibited by law from negotiating prices. In the United States, this means that pharmaceutical companies "can set prices freely," Danzon said, but she added that they are subject to mandatory rebate programs, such as that imposed by Medicaid. In addition, voluntary rebates may be negotiated by pharmacy benefit managers (PBMs) for private plans and Medicare Part D prescription drug plans. PBMs negotiate rebates off the list prices of drugs in exchange for preferred status on the plan formulary, which benefits a manufacturer by increasing their product's market share relative to competing products.[36] This has led to what Danzon described as "very competitive rebating" in large therapeutic classes with similar products (e.g., statins, antidepressants, insulins), because consumers are sensitive to the differences in copay between a preferred and non-preferred brand. Danzon said that PBMs are now using a fourth payment tier for specialty drugs that are differentiated in ways that limit substitution, and therefore limits negotiation for a rebate in exchange for formulary position.

In many cases, patients and providers also have a clear therapeutic preference for specific specialty products. Fourth-tier drugs often require prior authorization for coverage and have high coinsurance (25–30 percent). Depending on the total, the coinsurance would be prohibitive for most patients (e.g., 30 percent of a $50,000 drug is $15,000). However, Danzon noted that this high coinsurance is often covered by supplemental

[36] Many prescription coverage plans have tiered copay systems, with increasing patient copays for generic, preferred brand, and non-preferred brand products.

programs (e.g., low-income subsidies for Medicare and Medicaid, private Medigap plans, stop-loss limits on out-of-pocket payments, patient assistant programs, and coupons from pharmaceutical companies), so patient demand for specialty drugs is not fully price sensitive.

Products dispensed in a provider's office, such as vaccines or infused biologics, are generally covered by the patient's medical benefit. Products are purchased by physicians and billed to the patient's insurance. Medicare Part B, for example, reimburses "at the manufacturer's average sales price [ASP] plus 6 percent," Danzon explained. This creates an incentive to keep list prices high to provide a larger margin for the prescriber and discourages discounting (because discounts result in reduced ASP, which reduces reimbursement).

Reimbursement in Other Countries

In other countries, reimbursement is generally based on some combination of comparative effectiveness and cost-effectiveness, and external referencing to other countries (see Box 5). Danzon explained that external reference pricing (ERP) can "undermine appropriate price differentials

BOX 5
Reimbursement Prototypes Outside the United States

- ***Comparative effectiveness*** considers incremental gains in health versus comparable existing products. New products demonstrating increased health benefit can negotiate for a higher price. Otherwise, these are priced the same as existing comparable products.
- A ***cost-effectiveness analysis*** compares the incremental cost-effectiveness ratio of a new drug versus a comparator drug to a threshold. This threshold is generally a set cost per quality-adjusted life year, taking into account willingness to pay and other factors. Price is based on the incremental added value of the new product relative to competitor products.
- ***Enterprise resource planning,*** commonly used by European countries, takes into account the average or median prices for the same product in other countries. Enterprise resource planning is not related to any measure of value.

SOURCE: Danzon presentation, July 25, 2019.

between countries" because companies "raise prices or delay the launch of new drugs in smaller, lower-price referenced countries rather than lower the price in large, high-price countries" (Danzon and Epstein, 2012). She added that payers and companies are also finding ways around ERP by negotiating confidential discounts.

Pricing Trends in the United States

Danzon shared an analysis, which found that the prices for generic drugs decreased steadily from 2008 through 2016, while the prices for branded prescription drugs doubled during the same period (see Figure 4). Oncology drugs, orphan drugs, and specialty drugs are experiencing the largest price increases (IQVIA, 2019). An analysis by the Canadian Patented Medicine Prices Review Board found that United States prices for on-patent drugs are nearly three times that of Canada and other economically comparable countries (PMPRB, 2016). In summary, Danzon said, "on-patent drug pricing reflects reimbursement rules of insurance plans, which currently are not designed to constrain prices." A participant raised the issue of the decreasing availability of some generic drugs, which he said currently account for more than 80 percent of prescriptions. He added that some generic drugs have increased in price, and he emphasized the need to also consider generics in the discussion because different solutions may be required.

Linking NIH Funding to Value, Not Price

Danzon reiterated that cost is not the basis for price and said that even if the share of R&D cost attributable to NIH funding could be measured, it would not directly influence pricing. Instead, Danzon proposed an approach that links NIH funding "to a value-for-money limit on price, defined in terms of an incremental cost-effectiveness ratio." This could be done by setting a maximum price per quality-adjusted life year gained. She asserted that a value-based, cost-effectiveness analysis approach to pricing would create dynamic incentives for private R&D; reward incremental innovation; encourage efficient resource allocation; and ensure an appropriate return on investment for NIH and a range of other public subsidies for biomedical research (e.g., tax credits, insurance subsidies).

Sampat observed there are some new drugs that are both cost-effective and potentially unaffordable for many people (e.g., Sovaldi to treat HCV

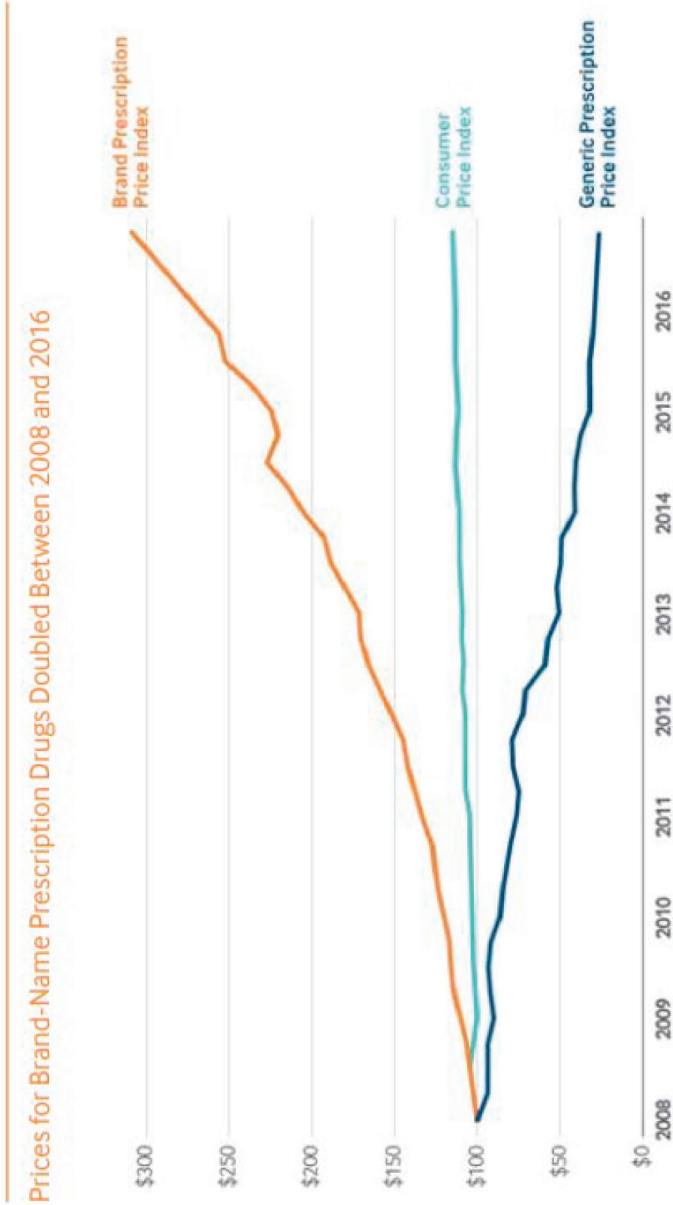

FIGURE 4 U.S. post-launch price growth for branded versus generic drugs, 2008–2016.
SOURCES: Danzon presentation, July 25, 2019, based on Kaiser Family Foundation analysis of data from Express Scripts 2015 Prescription Price Index.

infection). Danzon said that a cost-effectiveness threshold is not an "all-or-nothing approach" the way that march-in rights is. A cost-effectiveness threshold is "a ceiling on the price per unit of health gained, not an absolute ceiling on any price," she said. "The more effective the drug, the higher the price could be."

Sampat also asked how a cost-effectiveness threshold approach to pricing might affect technology transfer (e.g., to license an NIH-funded drug, the licensee would need to agree to certain cost-effectiveness thresholds). Stevens responded that "using a license agreement to control prices is a de facto antitrust violation." However, it is not clear whether this mechanism intended to lower prices would be deemed an antitrust violation. Danzon said that a cost-effectiveness threshold approach to pricing would not necessarily be part of a licensing agreement. Rather, it could be considered "general knowledge" that would be applied to reimbursement negotiations for most drugs, as most drugs benefit, directly or indirectly, from NIH-funded research.

Consumer Perspective on Prescription Drug Price Trends

Drug prices have increased significantly in recent years and current research suggests this trend will continue, observed Leigh Purvis, director of health services research in AARP's Public Policy Institute. Pharmaceutical manufacturers are focusing more on the development of orphan drugs, biologics, and personalized medicine products that usually command higher prices, and expensive specialty drugs constitute about half of the drugs currently in the late stages of the FDA approval process, she said. Importantly, the price of a product is not static once launched. AARP data indicate that the price of a brand name product often continues to increase at a rate that exceeds inflation (from 2- to 100-fold).

The cost of prescription medications is of particular concern for AARP's constituency, more than two-thirds of whom have two or more chronic conditions. Medicare data show that older adults enrolled in Part D use an average of 4.5 prescription drugs per month, Purvis said. She emphasized that this population often does not have the financial resources to pay for its prescriptions. "The median income for Medicare beneficiaries is just over $26,000 per year," she said, adding that 25 percent live on incomes of less than $15,000 per year and many have very limited savings.

High drug prices are also straining the public programs that older adults count on. Medicare Part B spending for drugs administered in the

provider's office was $32 billion in 2017, more than double that spent in 2005 ($13 billion). Purvis noted that Medicare Part B beneficiaries pay 20 percent of the covered amount, which leaves some beneficiaries "facing cost sharing of over $100,000." With regard to relying on supplemental coverage, she cautioned that costs are built back into the premiums, potentially influencing the affordability of these plans.

Medicare Part D spending on drugs dispensed at the pharmacy is nearly $150 billion per year. Even when enrollees have reached the out-of-pocket spending limit, she said, they are still responsible for 5 percent of their costs under catastrophic coverage. States are also feeling the impact of increasing prices in their Medicaid programs and must make difficult budgeting tradeoffs to try to fund prescription drugs and other services under Medicaid. Private insurance is not immune to the impacts of increasing drug prices, and Purvis said that employer-sponsored plans are also increasing prescription drug cost sharing through higher copayment tiers, coinsurance, and deductibles.

"High drug prices affect everyone," Purvis said, whether someone takes a prescription drug or not. Individuals pay directly, in full or in part, for a prescription drug, or they pay indirectly through insurance premiums and taxes that support public programs, including Medicare and Medicaid. Purvis said the majority of consumers (more than 80 percent) agree that prescription drug prices are too high, profits to drug companies are too high, rising health care costs are attributable to high drug prices, and legislative action is needed for change (Kaiser Family Foundation, 2019). The findings of several recent surveys show broad support for a range of potential solutions to improve patient access to affordable drugs, such as requiring advertisements to list drug prices, improving access to generic drugs, allowing CMS and states to negotiate for lower prices, and capping out-of-pocket costs. Purvis noted that consumers support biomedical R&D and understand that it is a costly process. They are less aware of their role as taxpayers in funding R&D, but Purvis observed that media attention to the issue is beginning to raise awareness.

In response to a question about recent policy action on drug prices, Purvis said that AARP is encouraged by the steps being taken toward transparency in pricing. She also noted that the Senate Finance Committee is debating legislation that would modernize aspects of Medicare Part D, and analysis by the Congressional Budget Office indicates that the bill would lower costs for beneficiaries.

A Path Forward

In closing, Purvis cautioned that current price trends are not sustainable for patients or payers. There is the potential to save billions of taxpayer dollars by reducing drug costs for public programs, including Medicare and Medicaid. Consumers want innovative new treatments, but many will not be able to afford new or existing drugs if rising prices are not addressed. Purvis emphasized the need for more consumer engagement, including raising the public's awareness of the role of its tax dollars in supporting the development of new drugs. She noted that the limited evidence thus far suggests that consumers support policy solutions that would ensure the affordability of drugs developed with taxpayer dollars. This fits with the trend toward solutions that build on the idea of fairness, she added.

Providing Access and Value for Low-Income Persons with Complex Medical Needs

"Amida Care is a Medicaid safety net health plan for persons with chronic illnesses living in New York City," said Doug Wirth, the company's president and chief executive officer. This special-needs health plan serves nearly 8,000 members who are living with or are at an increased risk for HIV and other co-occurring chronic conditions, including HCV infection, diabetes, hypertension, serious mental illness, substance use disorders, and cancers. He explained that the model of care focuses on ensuring that plan members have access to critical medicines and the support they need to achieve positive health outcomes and incur lower costs. The model incorporates integrated care teams, including health navigators and outreach workers to help address the social determinants of health; an in-house pharmacy team; wraparound services and treatment adherence support; and preventative care.

Wirth emphasized the importance of including members' voices in plan operations, especially with regard to pharmacy costs and medications. Member feedback is obtained from a member advisory council, a board of directors that includes two health plan members, town hall meetings and focus groups, a mechanism for submitting complaints, and satisfaction surveys. He also noted that about 8 percent of the staff are living with HIV.

The Amida Care model has been successful across a range of outcomes. Wirth said that 94 percent of plan members are in regular outpatient care, and 90 percent refill essential medications on a regular basis. He explained

that community health outreach workers follow up with members who miss appointments or drop out of care to make sure they are making the best use of their plan benefits. Providing this high level of care has led to more than 80 percent of the patient population with their HIV viral load suppressed to undetectable levels that correspond with lack of viral transmissibility. In addition, more than 1,000 patients have been effectively treated for HCV infection, and 25 percent of the 1,000 HIV-negative members are using the pre-exposure prophylaxis medication Truvada. Between 2008 and 2016, improvement in outcomes led to reductions in avoidable hospitalizations (by 70 percent); length of hospital stay (by 35 percent); and emergency department visits (by 50 percent), which Wirth said "resulted in $150 million in Medicaid cost savings to New York State Medicaid."

Wirth said that about 25 percent of members of the Amida Care health plan are co-infected with HIV and HCV, noting that in 2011, HCV co-infection became the leading cause of death for persons living with HIV in the United States. New HCV treatments have since become available. The newest direct-acting antiviral drug, Harvoni, which became available in 2014, has a very high cure rate with a shorter treatment regimen, Wirth noted, but costs between $95,000 and $160,000 per treatment. As a result, many managed care organizations have restrictive prior authorization criteria. He explained that in contrast, Amida Care advocated for HCV treatment of all co-infected individuals and worked to ensure access to treatment for members. More than 1,100 Amida Care members have now been effectively treated for HCV infection, with no reinfections, Wirth added. He pointed out that as more members were effectively treated of HCV, the overall need for health care decreased, resulting in reduced plan costs. In addition, "competition for preferred formulary status contributed to reductions in the cost per treatment, from $95,000 in 2015 to nearly $25,000 by 2019," Wirth said. Wirth suggested there are lessons to be learned about why the prices of the eight drugs for HCV infection decreased significantly since they were first launched.

Antiretroviral HIV Drugs

Single-tablet regimens (these combine two or more antiretroviral HIV medications in one pill) are simpler than taking multiple pills, Wirth said. The simplicity of taking a single pill has been shown to improve medication adherence, contributing to an increase in viral load suppression. Because the patient takes only one tablet, the number of antiretroviral prescrip-

tions has decreased. The cost per prescription has increased, however, as has the ingredient cost per single pill, leading to an overall increase in the cost of HIV treatment. From an outcomes perspective, Wirth stressed that treating chronic conditions is as much about delivery and support systems as it is about the medication. He illustrated with data showing the positive impact of targeted case management (e.g., wraparound support, care coordination) on outcomes for HIV-positive individuals treated with these high-cost specialty drugs (Brennan-Ing et al., 2016). This is important, he explained, because reducing reliance on facility-based care reduces total costs.

Financing Specialty Drugs

The ability of Amida Care to make specialty drugs available depends on the adequacy of Medicaid rates, Wirth said. He commended New York State Medicaid for negotiating HIV drug rebates directly with the manufacturers, which has expanded access, he said. He noted that Amida Care also pursues supplemental plan-based rebates through its PBM, as was done for HCV medications. Wirth stressed that it is much more effective for a state Medicaid program to negotiate for rebates with a drug manufacturer that can be applied across the program than for individual payers or PBMs to each negotiate with manufacturers for supplemental rebates.

Citing the successful health and financial outcomes associated with treatment and cure of HCV infection, Wirth recommended that government programs explore a "cost-of-cure approach" to funding drug development. The costs of large-scale access to specialty drugs could potentially be offset over time by the reduced use of health care.

Financing Antibacterial Drug Discovery and Development

The effectiveness of most classes of drugs on the market does not decline over time. For antibiotics, however, usefulness declines as drug-resistant bacteria emerge. Once an antibacterial drug enters routine use (sometimes even before), the target bacteria begin to evolve to combat the particular mechanism of action. Constant innovation is needed to keep pace with the emergence of new antibiotic-resistant strains of bacteria, explained Kevin Outterson. He noted that drug-resistant Gram-negative bacterial pathogens are of particular concern, according to the Centers for Disease Control and Prevention report *Antibiotic Resistance Threats in the United*

States, 2013 (CDC, 2013). The last new class of antibiotics against Gram-negative bacteria to be approved by FDA (quinolones) was discovered in 1962, he said.

Antibacterial Products in Development

As of June 2019, there were 42 antibiotics in development globally, only 11 of which are targeted to treat drug-resistant infections classified by the World Health Organization as global priority pathogens (PEW, 2019).[37] For perspective, Outterson said that there are more than 1,000 immuno-oncology products in development. As discussed earlier, few of the antibiotics in development will advance to become approved products.

An analysis of antibacterials approved by FDA from 2010 to 2014 shows that, although eight new antibiotics were approved, they were not the products urgently needed to treat resistant organisms (Deak et al., 2016). The analysis also found that most were transferred to a different company, often multiple times, over the length of development. Outterson noted that the bulk of the development was done by small companies (fewer than 100 employees), with larger companies entering at the commercialization phase.

Outterson also shared an analysis demonstrating that three-quarters of the antibiotics launched in the United States since 2009 are being sold at a loss (calculated with the R&D cost assumed to be zero [i.e., sunk]).[38] Noting the poor sales revenue of these drugs, Outterson hypothesized that the problem is one of economics, not science, and he suggested that the revenues from these products are too low to support sustainable R&D. To illustrate, he calculated the collective R&D spending of six of the public companies in the analysis to be more than $2.5 billion (i.e., total sunk cost). In total, the six companies have six FDA-approved products and several more in Phase 3 development. The combined market cap for the six companies, as of July 2019, was about $500 million. This means that these scientifically successful companies are collectively taking a $2 billion loss. In response to a question, Outterson noted that antibiotics administered intravenously in hospitals are covered under Medicare Part A as part of diagnosis-related group bundled payment. This approach to pricing is also detrimental to antibiotic innovation.

[37] For the list of global priority pathogens see https://www.who.int/medicines/publications/global-priority-list-antibiotic-resistant-bacteria/en (accessed September 23, 2019).

[38] Personal communication with Alan Carr, November 5, 2018.

The current antibacterial preclinical pipeline includes small molecule drugs and a range of innovative alternatives to traditional antibiotics, Outterson said. These include monoclonal antibodies, phages directed at select pathogens, and microbiome-based approaches. In addition, he said that 72 percent of the traditional antibiotic projects in preclinical development involve new molecular targets, new mechanisms of action, or new classes of drugs. Although the connection of these projects to NIH funding has not been analyzed, he said that "almost everybody in this field has some NIH funding in their background" as a doctoral student, postdoctoral fellow, or researcher.

CARB-X

Outterson listed a host of initiatives that are working to address antimicrobial drug resistance.[39] For example, from 2016 through 2018, NIH spent $1.4 billion on basic research, SBIRs, preclinical services, and other activities (including therapeutics, vaccines, and diagnostics) to combat microbial threats. Another initiative is CARB-X, which Outterson described as a case example of an innovative model for accelerating drug development.

CARB-X is a global, nonprofit partnership among the governments of the United States, the United Kingdom, and Germany. Funding from the United States comes through HHS, specifically the Biomedical Advanced Research and Development Authority (BARDA) and NIAID, and from the Wellcome Trust and the Bill & Melinda Gates Foundation. Addressing the need for antibiotics involves two overlapping approaches, Outterson explained. One approach is to reduce the demand for antibiotics through public health measures such as infection control, development of diagnostics, and stewardship of existing drugs to avoid the development of hard-to-treat drug-resistant strains. The other approach is to increase the supply of new therapeutics and restore or repurpose older products. Vaccines and microbiome modulators represent the overlap of these two approaches.

Outterson said that CARB-X is investing more than $500 million over 5 years (2016–2021) in funding to develop new products for priority pathogens, including therapeutics, diagnostics, vaccines, and microbiome-based

[39] Antimicrobial drugs treat infectious microorganisms including bacteria, viruses, fungi, and parasites. Antibiotics are antimicrobial drugs that treat bacteria. Antibacterial agents (e.g., antibiotics, disinfectants, antiseptics, heat) kill or inhibit the growth or reproduction of bacteria.

approaches. He noted that up to 20 percent of CARB-X funding supports the development of diagnostics for infectious diseases. Current diagnostics can take days to provide definitive results, he explained, and patients in urgent need (e.g., feverish and unconscious) are treated empirically with a broad-spectrum antibiotic until a diagnosis can be confirmed and a more specific antibiotic administered.

To date, $126 million has been awarded across 44 projects in 7 countries, and more than 15 other approved projects have funding pending. He added that all funding awards are nondilutive. CARB-X funding support extends through the end of the Phase 1[40] clinical trials, with the expectation that the companies will then attract other public and private funding to support Phase 2 and 3 development. Outterson added that CARB-X, through its funding program, has "an amazing viewpoint" of the current state of antibacterial drug development, and is using anonymized information to study the social science aspect of drug resistance (i.e., the impact of human behavior).[41]

Innovation, Access, and Stewardship

In addition to innovation and access, stewardship is a key element of antibiotic drug development, Outterson said. As discussed, antibiotic usefulness can decline over time due to overuse. For success, these three elements—innovation, access, and stewardship—must come together in a delicately balanced tripod (see Figure 5). He explained that prioritizing stewardship can inhibit access and slow innovation, overemphasizing innovation can lead to high prices and limit access, and providing access without proper stewardship promotes antibiotic resistance (Hoffman and Outterson, 2015). CARB-X contractually requires companies that are funded to "prepare a nonconfidential stewardship and access plan no later than the pivotal clinical trial," Outterson explained. When a drug is approved by FDA, the plans are made public (on the CARB-X website) and include information on pricing, licensing strategy, commercialization plan, and access strategy. In response to a question, he said that the contractual requirements were refined during a year-long process incorporating input

[40] Clinical trial in a small number of patients in which the toxicity and the dosing of an intervention are assessed.

[41] See the Social Innovation on Drug Resistance (SIDR) Postdoctoral Program at https://www.bu.edu/ihsip/our-work/sidr (accessed September 23, 2019).

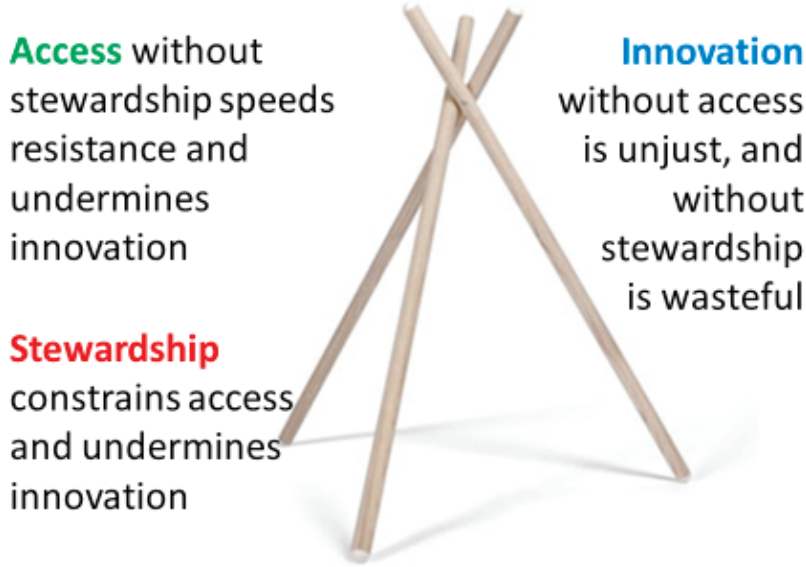

FIGURE 5 The antibiotic tripod.
SOURCES: Outterson presentation, July 24, 2019; Hoffman and Outterson, 2015.

from funders, potential awardees, and other stakeholders. He noted that there is an access rights provision, modeled after the Bayh-Dole Act, which applies to the intellectual property discovered using CARB-X funding.

Pricing Antibiotics Based on Value

Outterson said that industry has engaged with the National Institute for Health and Care Excellence in the United Kingdom to address low prices for antibiotics. One approach being tested in the United Kingdom is a "Netflix subscription model" in which the government would pay a fixed, value-based price per year for access to a company's antibiotics, regardless of level of use.[42] Similar models that would delink profit from volume sold and instead focus on societal value of the product are also under consideration in the United States. This is a "radically different way of paying for the drugs," Outterson said, but it is not that unlike prepaying for other interventions that might not be needed (e.g., fire protection equipment in a building is

[42] See https://www.gov.uk/government/news/development-of-new-antibiotics-encouraged-with-new-pharmaceutical-payment-system (accessed September 23, 2019).

paid up front even though it might never be used, rather than paid for only if it is needed during a fire).

Danzon observed that a subscription approach would be practical to implement in the United Kingdom because the National Health Service is a single payer system, and she asked how it might be implemented in the United States. Outterson agreed that the complex system of payers in the United States adds to the challenge. It would not be practical to negotiate separately with the hundreds of payers or each of the thousands of hospitals and other providers. One approach proposed recently in the U.S. Senate is an antibiotic market entry reward.[43] A company would sell its drug but receive a government payment for agreeing to stricter parameters for marketing, stewardship, and other aspects. Even in the face of low sales revenue, Outterson explained, a manufacturer would receive a significant payment that could both recoup some sunk costs and support post-approval studies.

Ledley raised the possibility of bulk purchases to provide a bolus of cash to companies developing antibiotics, similar to purchasing for the Strategic National Stockpile (SNS). Outterson noted that buying in bulk generally lowers the price, which is not the goal for antibiotics. In addition to funding preclinical and clinical antibiotic research, BARDA does purchase antibiotics for the SNS, he said, but not in quantities sufficient or regular enough to sustain a company.

STRATEGIES AND POLICIES TO FACILITATE TRANSLATION

Having reviewed the current state of technology transfer of NIH-funded research, panelists and participants examined potential strategies and policies to facilitate the translation of federally funded biomedical research into innovations in drug development. The discussion was moderated by Jennifer Moore, founding executive director of the Institute for Medicaid Innovation and research professor at the University of Michigan Medical School.

Panelists discussed:

- reducing risks and costs and improving returns in drug development;
- government-funded biomedical research at the U.S. Department of Defense (DoD); and opportunities to partner with DoD in common interest areas;

[43] The most recent version of this legislation at the time of the workshop was the Developing an Innovative Strategy for Antimicrobial Resistant Microorganisms (DISARM) Act of 2019 (S. 1712).

- public–private partnerships, precompetitive collaborations, and research consortia;
- repurposing existing approved products for secondary uses; and
- reducing the variance at each step of the drug development process and addressing efficiency "holistically," at a systems level.

Reducing Risks and Costs and Improving Returns in Drug Development

Although there are different ways to calculate the time and costs of bringing a product to market and ongoing debate about the resulting estimates, it is clear that "it is very, very expensive and risky to develop drugs," said Steven Galson, senior vice president of Global Regulatory Affairs and Safety for Amgen. He stressed that the cost to develop one new drug has been estimated to be as high as $2.6 billion (DiMasi et al., 2016), about 90 percent of development programs fail, and late-stage failures are particularly costly. Despite improvements in efficiency, developing and manufacturing new therapeutic modalities, especially biologics, has become more complex, and total costs have more than doubled over the past 10 years, he said.

Galson explained that clinical success rates vary somewhat by therapeutic area but have remained relatively static overall, with limited improvement in late-stage probability of success (Dowden and Munro, 2019). He noted that the therapeutic areas with the highest failure rates (e.g., cardiovascular, nervous system) are the same areas for which there are significant public health needs for drugs (e.g., heart disease, Alzheimer's disease). As an example of an unexpected late-stage failure he mentioned the recent decision by Amgen and Novartis to discontinue pivotal Phase 2 and 3 clinical trials of an Alzheimer's prevention drug.[44]

In association with increased costs and static success rates, returns on investment in pharmaceutical R&D continue to decline, whether measured as productivity (i.e., approved new products) or dollars (Deloitte, 2018; Scannell et al., 2012). "The industry is still profitable, but the profitability has been decreasing over time," Galson said, adding that this is an important factor to keep in mind when discussing drug pricing. He also pointed out

[44] See https://www.amgen.com/media/news-releases/2019/07/amgen-novartis-and-banner-alzheimers-institute-discontinue-clinical-research-program-with-bace-inhibitor-cnp520-for-alzheimers-prevention (accessed September 23, 2019).

that private-sector investment in biopharmaceutical R&D is nearly twice the total NIH budget (PhRMA, 2017).

To help increase rates of success and reduce costs in drug development, NCATS, FDA, biopharmaceutical companies, and other stakeholders are looking to a range of new technologies, process improvements, and collaborations, Galson said. He mentioned several examples, including advanced computational power and analytics, genetics and genomics, biomarkers, targeted drug delivery, regenerative medicine, nanomedicine, public–private partnerships, and new regulatory pathways.

A participant suggested the need to develop different approaches for different types of drug development, observing that R&D is only a small portion of a biopharmaceutical company's total expenditures, while it constitutes a very large portion of total expenditures for a small start-up company. The extent of the impact of reducing development costs would be different for each segment of the industry. Galson agreed and said that "there is not a one-size-fits-all solution to any of these issues." Danzon pointed out that the study of R&D costs cited by Galson (DiMasi et al., 2016) looked at expenses for large companies. Data from IQVIA show that less than 20 percent of the drugs approved by FDA were developed by large pharmaceutical companies, while more than 70 percent were the products of small companies. The limited available data suggest that the R&D costs of smaller companies are "dramatically lower" than those of large companies. Danzon suggested this is due in part to the different therapeutic categories each is pursuing but also because overhead and acquisitions costs are built into the costs reported by large companies. These differences contribute to the difficulty of determining a representative average cost of R&D. Galson agreed and added that many small companies pursue orphan indications, which take a very different development path from, for example, a 30,000-person cardiovascular drug clinical trial. David Dilts, managing partner for Dilts+Partners, LLC, and adjunct professor at Vanderbilt University and Oregon Health & Science University, pointed out the need to also account for the costs associated with small companies that fail to develop any product.

Meeting U.S. Department of Defense Medical Support Needs

The DoD medical R&D program is invested in combat casualty care; military infectious diseases (e.g., malaria, dengue, diarrheal diseases, other endemic infectious disease in deployment areas); military operational medi-

cine, including psychological health (e.g., posttraumatic stress disorder, suicide prevention) and physiological health and resilience (e.g., military performance in environmental extremes, nutritional interventions); and rehabilitation and regenerative medicine (for wounded, ill, or injured service members), said Terry Rauch, acting deputy assistant secretary of Defense for Health Readiness Policy and Oversight. He noted that the last category includes a significant investment by DoD in service members who are non-deployable due to medical conditions (e.g., musculoskeletal injuries experienced during training).

Rauch mentioned several areas of ongoing research, including ways to better empower combat medics to deliver care to a high volume of trauma casualties, such as burn injuries, and ways to utilize artificial intelligence and autonomous systems to deliver battlefield care. Moore asked how DoD might partner with other agencies, academia, or industry to build efficiencies in common interest areas. First, Rauch encouraged potential partners to attend the annual Military Health System Research Symposium. He said that this yearly event provides a venue for nearly 3,000 scientists from DoD, academia, and industry to present their research on topics relevant to the mission of military health. Second, he noted that potential extramural partners should also look for DoD program announcements on Grants.gov, as a significant amount of funding is dedicated for competitive extramural grants.[45]

C-Path: Collaborating to Accelerate Medical Product Development

Several speakers at the workshop discussed public–private partnerships as an approach to accelerating product development. The Critical Path Institute, or C-Path, is a public–private partnership established in 2005 to facilitate the sharing of expertise and data to help derisk drug development, said Lynn Hudson, chief science officer for the organization. C-Path manages 15 consortia that collaborate with more than 1,500 scientists and 90 organizations. These include consortia that focus on diseases, such as Alzheimer's, Parkinson's, and multiple sclerosis, and crosscutting consortia that address issues such as predictive drug safety testing.

Hudson showed examples of some of the regulatory tools developed by the consortia. The Patient-Reported Outcome Consortium, for example, has developed three FDA-qualified patient-reported outcome instruments:

[45] See https://www.grants.gov (accessed September 23, 2019).

a symptom assessment questionnaire for non-small cell lung cancer; daytime and nighttime symptom diaries for asthma; and a symptoms scale for major depressive disorder. Companies developing drugs for these conditions can use these tools to collect and submit consistent patient-reported outcome data. This shortens the review time because it eliminates the need for FDA to evaluate each company's instrument in addition to evaluating the associated patient data. There are several data programs, including a Data Collaboration Center that facilitates sharing of clinical, genomic, phenotypic, and non-clinical data. C-Path has also contributed to the development of therapeutic area data standards, which Hudson said also contribute to a more streamlined review of applications.

Hudson explained that data received by C-Path are mapped to a standard and pooled for use in addressing a range of research questions. Data in the Alzheimer's database, for example, were used to develop a disease progression model that then led to the development of a clinical trial simulation tool to aid in trial design. The Multiple Sclerosis Outcome Assessments Consortium has developed and is working to qualify performance outcome measures of disability that can be used as primary or secondary endpoints in clinical trials (e.g., walking speed, manual dexterity). The Polycystic Kidney Disease Outcomes Consortium used aggregated data to model total kidney volume with disease progression. This was used to develop total kidney volume as a qualified prognostic biomarker and potential surrogate endpoint for clinical trials.

For some areas, such a neonatal drug development, data are extremely limited. Few clinical trials are conducted in neonates, and "almost all drugs used in neonatal intensive care units are used off label," Hudson said. The International Neonatal Consortium is working to identify data needs and collection methods, facilitate data sharing, and develop master protocols for platform trials. There are "huge gaps of knowledge" that Hudson said NIH studies could fill, including studies of the natural history and underlying pathology of neonatal conditions; identification and validation of biomarkers; collection and analysis of real-world data (e.g., EHR); and development of innovative clinical trial designs.

Repurposing Compounds for New Therapeutic Uses

One strategy to improve efficiency and lower costs in drug development is repurposing existing approved products for secondary uses. Christine Colvis, director of drug development partnership programs at NCATS, described three NCATS programs focused on repurposing.

The New Therapeutic Uses program facilitates collaborations between pharmaceutical companies, which provide information about and access to approved, proprietary compounds for further study, and academic researchers, who identify and study potential new indications for those compounds. Template agreements serve as a translational strategy to streamline the process of setting up the public–private partnerships. Products for repurposing must have a known mechanism of action and acceptable safety data from a completed Phase 1 clinical trial. Colvis noted that products offered for repurposing studies have often been studied through Phase 2 or 3 but were discontinued for business or scientific reasons (e.g., lack of efficacy for the original indication). NCATS posts products being made available for studies on its website[46] and provides funding opportunities for researchers to support clinical trials.

Another program provides the opportunity for researchers to collaborate with NCATS intramural scientists. This is a true, milestone-driven, synergistic collaboration, Colvis said, and no money is involved (no funding is available, no fees are charged). As a collaborator, NCATS can offer access to resources, technology, and automation that are often not readily available to academic researchers (e.g., 3-D tissue printing, stem cell laboratory), along with program management, industry, and medicinal chemistry expertise. External collaborators bring biomedical subject-matter expertise; targets, probes, or compounds; data; and other resources. Colvis described the process as agile because the intramural program can redirect funds to projects as needed, allowing NCATS to take more risks.

Finally, Colvis said that the Biomedical Data Translator program is designed to integrate data from clinical discovery and routine clinical care (e.g., EHR), patients, and basic science discovery research (e.g., mechanistic studies, molecular characterization), and feed it back out to inform clinical medicine and biomedical research. The intent is not simply to provide a data access portal, Colvis said, but to computationally mine the data to recognize connections and make new inferences that will advance translational research.

Infrastructure for Drug Development Innovation

Dilts said that there are many areas for improvement in efficiency across the drug development pathway, especially in the activities leading

[46] For the list of available industry-provided assets, see https://ncats.nih.gov/ntu/assets/current (accessed September 23, 2019).

up to the launch of a clinical trial. There is significant variance in each step of the drug development process, and controlling that variance is key to increasing efficiency. For example, he showed an analysis that suggests a link between clinical trial development time and successful accrual; specifically, a shorter development time is associated with a greater likelihood of achieving accrual goals. He said science changes over time, and if it takes too long to launch a trial, the field will have moved on and the trial may no longer be perceived as cutting edge. He said that accrual then falters, and if the accrual goals have not been achieved, all of the effort leading up to launch will have been wasted. Another area with major variance is the time spent in scientific review and IRB approval. He concurred with others that working together is essential for success and suggested that one approach to address these variances would be to form precompetitive consortia to develop standards. He noted that there are lessons to be learned from the successes in other industries.

Partnering for Translational Research Success

Following the panel remarks, partnerships as a strategy to facilitate translation (including public–private partnerships as well as precompetitive collaborations among private-sector companies) was a main topic of discussion.

Precompetitive Collaborations

In the face of rising manufacturing costs, Reed Tuckson, managing director of Tuckson Health Connections, LLC, asked whether companies might collaborate to share manufacturing knowledge and engage NIH translational science in solving common manufacturing problems, instead of each company developing proprietary manufacturing systems. Galson responded that there are public–private collaborations that have advanced manufacturing and development processes, as well as collaborative activities run by professional organizations. He said, however, that setting drug prices "is a complicated interplay between the various parts of the health care system and the drug industry" without one simple solution, such as reducing manufacturing costs. Dilts mentioned the Integrated Manufacturing Technology Roadmap Initiative, which established goals for advancing manufacturing technology and then identified which stakeholders had the appropriate capabilities and expertise to collaborate on solutions to achieve

a given goal. The initiative also identified numerous common problems across stakeholders. He added that a precompetitive research consortia approach provides a good return because all members contribute part of the cost but reap the full reward of the research.

Diana Pankevich, director for science policy and advocacy at Pfizer, said that the pharmaceutical industry is willing to partner in the precompetitive space on critical issues, and she mentioned TransCelerate BioPharma[47] as an example of a pharma-led cross-industry collaboration to develop solutions that improve drug development efficiency. She noted the need for more opportunities for stakeholders to come together to innovate. She suggested a fellowship-style program as a collaborative mechanism where industry scientists might spend time at NIH or FDA working on key issues. Galson agreed that more collaboration is needed and precompetitive collaborative approaches, like TransCelerate and the Clinical Trial Transformation Initiative,[48] are useful for tackling efficiency issues in drug development. Dilts cited the Massachusetts Institute of Technology Leaders for Manufacturing program as an example of an academic–industry partnership that integrates management and engineering education and research to help solve manufacturing problems.[49]

Ian Kremer, executive director of the Leaders Engaged on Alzheimer's Disease Coalition, agreed that there are system-wide problems and many opportunities for precompetitive collaboration on solutions. He proposed an analog of the Prescription Drug User Fee Act (PDUFA)[50] for NCATS or NIH, in which a user fee paid by companies, along with appropriations, might fund research into high-priority systems improvements for the benefit of all users. However, Colvis and Kremer noted that such an approach would likely be prohibited under current statutes.

[47] This is a nonprofit made up of major biopharmaceutical companies, with the vision of simplifying and accelerating the R&D of innovative new therapies.

[48] It is a public–private partnership with more than 80 organizations from government agencies, industry representatives, patient advocacy groups, professional societies, investigator groups, academic institutions, and other interested parties across the clinical trial enterprise.

[49] Now known as the Massachusetts Institute of Technology Leaders for Global Operations program. See https://lgo.mit.edu (accessed September 23, 2019).

[50] The Prescription Drug User Fee Act allows FDA to collect fees that are used to expedite the drug approval process. See https://www.fda.gov/industry/fda-user-fee-programs/prescription-drug-user-fee-amendments (accessed September 23, 2019).

Public–Private Partnerships

Galson pointed out that C-Path has created "dozens of public–private partnerships over a number of decades" involving FDA, NIH, academia, nonprofit organizations, and the private sector, which contribute significantly to finding solutions that lower costs of product development. He said, however, that much more could be done if there was more funding for NCATS and for FDA to dedicate to partnerships.

Rauch emphasized the importance of relationships. He said that DoD collaborates with NIH and the U.S. Department of Veterans Affairs on issues such as suicide, posttraumatic stress disorder, and traumatic brain injury, often co-founding a consortium to focus on drug development for a specific condition. In addition, the military health care system has about 9 million beneficiaries across the military treatment facilities and clinics, and Rauch said this represents an opportunity for academia and industry to partner with clinical investigators in military treatment facilities. Colvis emphasized the importance of having a champion within the pharmaceutical company who is committed to the partnership. But if that champion leaves the company, the partnership can be at risk of "unraveling," she added. It is also essential, she continued, to be able to show potential partners how the collaboration is beneficial. Once a partnership is established, it is important to include professionals who can manage the process (e.g., project managers, systems engineers), Dilts said, adding that the scientists providing the expertise in the partnership are generally not trained to manage a collaborative project with milestones. Colvis agreed and added that a good project manager keeps the program on track, allowing the experts to focus on the science.

Lana Skirboll, vice president of academic and scientific affairs at Sanofi, observed that there are development areas that NIH is well suited to collaborate on, and other areas perhaps less so, and asked whether funds and resources should also be provided to FDA for a translational science innovation center. Dilts referred to the drug discovery, development, and deployment map presented by Austin (see Figure 1) and said it is necessary to look at all of the steps in development to identify bottlenecks and gaps across the whole span of the process and determine which organization has the expertise to fill each gap (e.g., NIH, NIST, FDA).

Additional Strategies to Facilitate Translation

Moore called on panelists to share their personal recommendations for strategies to facilitate translation and increase the efficiency of drug development. Galson emphasized the value of the many National Academies activities convened to consider all aspects of biomedical product development. Hudson called for more funding for NIH to be able to support the types of translational science studies that are not rewarded by tenure and publishing structures. She agreed with Skirboll about the role of FDA in stimulating translational activities and the need to fund NIH and FDA to work together on these issues. Colvis noted the earlier discussion of the need to recognize the differences among product developers and sectors. She recommended finding ways to empower stakeholders to identify and take on appropriate roles and actions for maximum impact. Dilts emphasized the need to address efficiency "holistically" at a systems level, identifying the role and responsibility of each stakeholder to form more productive high-level collaborations and sub-collaborations.

POTENTIAL POLICIES TO ENSURE AFFORDABLE ACCESS

In the second strategy session of the workshop, panelists and participants discussed new ideas, opportunities, and potential public policies that could help ensure that the public has affordable access to innovative drugs that have benefited from federal investments. The session was moderated by Tuckson.

Panelists discussed the potential for:

- creating a separate entity to negotiate the pricing aspect of intellectual property transfer;
- addressing pricing at the point of technology transfer;
- reinstating the reasonable pricing provision in the CRADA;
- reforming the patent system, including modifying the inventiveness standards for patents, restricting continuation applications, and improving the existing patent challenge system;
- implementing stricter monitoring of disclosure of federal funding in patents and penalties for lack of disclosure; and
- managing pricing via licensing strategies, through action under current law or general drug pricing and access reform.

Pricing of Taxpayer-Funded Drugs

Mitchell shared his perspective on affordable access to drugs as both the founder of Patients for Affordable Drugs and a person living with multiple myeloma for the past 9 years. Multiple myeloma is incurable, he explained, but it can be managed with medication, and twice per month, he receives an infusion of drugs that are priced at more than $600,000 per year. While Mitchell said he has good health care coverage and could afford the out-of-pocket costs of his treatments, he echoed the sentiment voiced throughout the workshop that "drugs don't work if people can't afford them." To illustrate, he said that early in his treatment he was given Revlimid (a modern derivative of thalidomide, a drug first used in the 1950s in Europe), which cost him $250 per month out of pocket. In contrast, the median out-of-pocket cost for Revlimid for Medicare beneficiaries was $15,000 per year, which is about half the median annual per capita income. Paying for needed prescription drugs "is bankrupting some of us," Mitchell said; when people cannot pay and resort to rationing or skipping treatments, high drug prices can literally kill them. Patients for Affordable Drugs was launched out of these stories and experiences to give voice to those who might not be able to afford to survive. The stories of nearly 20,000 patients are shared on the website.[51]

Costs and Prices

Mitchell acknowledged that pharmaceutical R&D is expensive but added that "multiple studies show there is no correlation between the cost of innovation and the price of a drug." Mitchell expressed concern that the often-cited estimate of $2.6 billion as the cost of developing one new drug (DiMasi et al., 2016) was based on a study that "companies paid for, supplied the data for, and won't reveal the underlying data for, citing trade secrets." He added that other studies have estimated a much lower cost. In addition, as discussed throughout the workshop, much of the early research that leads to new drugs is supported by NIH funding, which comes from taxpayer dollars. "Tax-advantaged dollars flow through research foundations, academic medical centers, patient organizations, and research and development tax credits," he said.

[51] See https://www.patientsforaffordabledrugs.org (accessed September 23, 2019).

To illustrate, Mitchell described the development of LentiGlobin BB305, a gene therapy that is currently in clinical trials for the treatment of sickle cell disease; Mitchell suggested that it could be a cure. According to Mitchell, $300 million of taxpayer money has been invested thus far. If approved, current pricing estimates have ranged from $500,000 to $2,000,000 for treatment with a therapy that Mitchell emphasized was developed with taxpayer support. Similarly, he said $200 million in taxpayer money was invested through NIH funding in the basic research done at the University of Pennsylvania that led to the development of CAR-T therapy. In 2012, when Novartis licensed the CAR-T technology from Penn, Mitchell said that clinical trials for the first CAR-T therapy, Kymriah, had already been conducted. The price for treatment with Kymriah, he said, is $475,000. Yescarta, another CAR-T therapy, was acquired by Gilead when it purchased Kite Pharma for nearly $12 billion. However, "SEC filings showed $321 million in research and development costs by Kite prior to the sale," Mitchell said, which demonstrates that the purchase price of the company and its technology was based not on the cost of research, but on the anticipated future returns from sales of a high-priced product.

Potential Solutions to the "Pricing Crisis"

Drug companies are businesses that seek to maximize profits. There are hundreds of clinical trials under way for new gene therapies, and Mitchell said that consumers cannot afford to pay the prices these products are currently being marketed for. While these new therapies can lead to significant savings to the health care system, he said this is not an ideal benchmark, as existing alternatives are also frequently overpriced. Mitchell said that truly innovative products should result in profits for manufacturers, but the system is "way out of balance," and high drug prices are bankrupting consumers, negatively affecting health outcomes, and costing lives.

Mitchell offered several potential solutions for discussion:

- **"Congress should establish an entity" to deal with pricing issues.** NIH is focused on conducting and collaborating on cutting-edge science to meet the health needs of the nation. It does not and should not have responsibility for pricing. During the discussion, it was proposed that this entity could reside elsewhere within HHS.
- **Address pricing "at the point of technology transfer, not after the fact."** This would provide predictability for product manu-

facturers and restore needed balance across stakeholder (including taxpayer) investments, manufacturer profits, and affordability and access for consumers. This mechanism should take into account an understanding of the risk and the full value of the drug.

- **Consider a variety of pricing strategies that could "strike the right balance to protect innovation and maximize public health."** Examples included setting a cost-effectiveness threshold and reference pricing (discussed previously by Danzon).
- **"NIH should reinstate the reasonable pricing provision in every CRADA and exclusive licensing agreement."** The concerns that this clause had a "chilling effect" on cooperation are unsubstantiated.

Drug pricing should not be based on what a patient is willing to pay to survive, Mitchell concluded. Strategies are needed that define what companies should earn for new products, especially products developed with taxpayer support, and "that number cannot be unlimited," he said. Mitchell also called for better tracking of patents and intellectual property that result from taxpayer-funded research.

Establishing an Entity to Negotiate Price at the Point of Technology Transfer

Participants further discussed creating a separate entity to negotiate pricing issues at the point of intellectual property transfer, as Mitchell had suggested. Sarpatwari commented that addressing pricing is not the role of NIH, but there should be an entity for this, perhaps similar to how the technology assessment bodies fulfill this role across Europe. Kesselheim agreed that pricing should be addressed upfront to set expectations. Merrill suggested that an entity within HHS would be most appropriate to address pricing because HHS has the payer's perspective.

A contractual approach, where access provisions are included in technology transfer or grant making, for example, requires "enough commercial pull in the market" (i.e., interest in the science). Carino pointed out that philanthropic funding often precedes NIH funding. For other areas of science with very weak commercial signals of value (e.g., antibiotics, rare disease research), she said that philanthropic donors are often left looking for scientific efforts to support, and she noted her concern that including access provisions in contracts would likely be another barrier to encouraging this science. For example, disease-related foundations have been considering how access and affordability might be incorporated into their grant-making process and have

found it to be very difficult to implement, she said. She suggested reaching out to the disease philanthropy community to learn from their experiences. Mitchell agreed and said that technology transfer only works if someone wants the technology. However, he suggested that limitations are needed that clarify that a CRADA is a partnership and the goal of NIH as a partner is to ensure that the "public investment maximizes public health." External partners will have to "play ball" if they want access to "the value that taxpayers are creating with their investment in early, high-risk science."

Sarpatwari raised the issue of the CRADA reasonable pricing clause, which he described as "ambiguous." He added that a Materials CRADA is "not the typical type of collaboration that one would expect would lead to drug products." He explained that the reasonable pricing clause was removed in 1995, and the Materials CRADA was introduced in 1996. He shared data showing that although the total number of CRADAs increased starting in 1996, the number of standard CRADAs remained fairly steady for more than a decade. This illustrates the importance of understanding "what actually happened" when a condition is imposed, he said.

Improving System Performance and Supporting Emerging Innovative Companies

Access and affordability are key concerns for FasterCures in pursuing its mission to build a medical research system that is efficient, effective, and driven by patient needs, said Carino of FasterCures (a center of the Milken Institute). She described two examples of ongoing research efforts related to affordable access.

Advancing a High-Performing System

Essential information when working to build a high performing health system is knowing "if and when the system is working optimally for patients," Carino said. However, there are no commonly used metrics for assessing the performance of the health system "from end to end." To address this, FasterCures assembled a stakeholder group "to define and clarify the goals of an ideal system" and develop or modify existing metrics to identify bottlenecks and misaligned incentives and measure the overall performance of the biomedical innovation system.

At a workshop in February 2019, the stakeholders developed a shared vision statement; "a high-performing system should be a learning health

care system that improves health outcomes for all," Carino said. The first step of the project will be to provide data on the state of the system to policy makers, and Carino said that FasterCures has partnered with RAND Europe to review the existing frameworks, domains, and indicators in the system. A workshop was also held to consider potential elements of an innovation scorecard, and future work will focus on issues such as accountability and resource allocation. Results of the RAND review and the workshop are expected to be released in fall 2019, and Carino previewed some of the findings. The review identified focus areas for achieving the vision, including "collaboration and transparency, efficiency, market environment, patient centricity, equitable access and use, innovation and productivity, and capacity."

Tuckson asked whether more public-sector research is needed to define what "value" means to patients. Oftentimes, Carino responded, the evidence needed to assess health technology does not exist in a form suitable for the assessment at hand. She suggested that government, philanthropic organizations, industry, and other organizations can contribute evidence to help fill the data gaps. She referred participants to an op-ed she recently coauthored on the role of the Patient-Centered Outcomes Research Institute in identifying biomedical research that is of value to patients (Carino and Boutin, 2019).

Incubator Project

FasterCures, with the Center for Financial Markets (another Milken Institute center), launched an incubator in spring 2019 to support emerging drug development organizations by "advancing new business models and financing models." Carino said that some of these are mission-oriented public benefit corporations that are prioritizing affordability. Examples include Paradigm Shift Therapeutics, developing affordable cancer therapies, and Audacity Therapeutics, working to repurpose drugs for new indications. There are nonprofit drug developers, including the Bill & Melinda Gates Foundation Medical Research Institute, which is focused on maternal and child health in lower- and middle-income countries, and nonprofit organizations that provide venture funding for drug development (e.g., Alzheimer's Drug Discovery Foundation, CureDuchenne). Carino noted that disease-focused nonprofit organizations are often willing to invest in earlier-stage research and accept higher risk than traditional investors. Payers also participate through research subsidiaries. For example, Clover

Health, a Medicare Advantage Plan, has launched Clover Therapeutics in partnership with biopharmaceutical companies.

The incubator also helps these emerging companies partner with large biopharmaceutical companies to facilitate development, manufacturing, and commercialization of their innovative products. This is especially important, Carino said, because many large companies are deprioritizing programs due to uncertainties about commercial potential and reimbursement. A high-performing system will bring diverse organizations together around shared goals and aligned incentives, she concluded.

Potential Areas for Reform

Amin listed key areas where patent reform is needed and shared his suggestions for action:

- **"Modify the inventiveness standards for patents."** A clear definition of what is truly inventive could allow early research funded by NIH to be cited as prior art, Amin said, and might prevent some of the "overpatenting" of drugs later. As an example, he said that the patentability standard for obviousness has become very narrow, and challenging a patent based on obviousness is extremely difficult. "The patent system is being corrupted" by modifications that are not inventive or innovative. Thomas disagreed that most patent application claims for different formulations or combination therapies are obvious. He said persuasive cases have been made by experts that most are very complex formulations and combinations "that no skilled artisan could have come up with." However, Mitchell said that one of the reasons Revlimid (approved in the United States in 2005 for multiple myeloma) still has no competition is a method of use patent for the combination of Remlivid and the steroid, dexamethasone. He observed that practitioners were administering dexamethasone with Revlimid long before Celgene applied for the method of use patent on it (i.e., it was clearly obvious).
- **"Restrict continuation applications at the USPTO."**[52] Continuations allow patent applicants to keep refiling applications in response to evolving competition, Amin said.

[52] Continuation applications are new patent applications that make additional claims related to the still pending "parent" patent application.

- **"Maintain and improve the existing challenge system."** The America Invents Act modified patent law to allow challenges to patent validity, Amin noted.
- **"Implement a stricter monitoring system that ensures better disclosure for federal funding in patents."**
- **"Implement a penalty for lack of disclosure of federal funding in a patent."** Amin suggested that the penalty could be the surrender of a patent right, or required licensing to a generic manufacturer.

Amin also mentioned some of the patent reforms in proposed legislation, most of which are intended to increase transparency (e.g., requiring patent transparency for biologics; improving quality and transparency of and removing invalidated patents from the Orange Book).

In closing, Amin questioned whether the patent system is really "the best incentive model for drug development and affordable access," adding that only a small percentage of company revenue can be attributed to new products. The majority of revenue is associated with repurposed products or technologies. In addition, Amin called for more proportional exclusivities, noting that not everything belongs in the patent system.

Options for Ensuring Affordable Access

Kesselheim offered four potential strategies to address the affordability of these products:

- **Pricing and access via licensing.** Per the Bayh-Dole Act, inventors and their employers may retain ownership of patents awarded based on federally funded research, negotiate licensing of that intellectual property, and collect royalty payments and equity interest. Kesselheim noted that this can bring billions of dollars into the university, although licensing agreements generally do not include pricing or access requirements. He suggested several models for managing pricing and access via licensing.
  - The Universities Allied for Essential Medicines (UAEM) model.[53] This model "advocated for technology transfer offices to include international access provisions when licensing their

[53] Through a grassroots approach, UAEM ensured that an HIV drug discovered at Yale was made accessible to individuals in low-income countries.

patents to private companies for development," Kesselheim said. He asked if similar provisions could be included in such contracts related to ensuring reasonable pricing. He said there are limitations to applying this model to the U.S. market, including the fact that the markets targeted by UAEM were not generating revenue for companies.

- The Reasonable Pricing Clause model. As discussed earlier, in 1989, NIH CRADAs included a reasonable pricing clause, which Kesselheim said was "implemented poorly" and was withdrawn in 1995 after pushback from industry. He reiterated that "there is no objective evidence" that the reasonable pricing clause had a "chilling effect" on CRADAs. NIH could therefore consider whether a Reasonable Pricing Clause could be resurrected and included as a standard policy for organizations that receive its grant funding.
- National Childhood Vaccine Injury Act model.[54] Kesselheim suggested that new legislation could be passed to establish an excise tax "for all drugs approved in which at least one patent declares government support." Proceeds could be returned to NIH to continue the cycle of funding the discovery of innovative treatments. Alternatively, legislation could set a price ceiling, as suggested by Danzon, based on a cost-effectiveness analysis or another threshold. This approach could be impactful, as data in a recent publication by Kesselheim and colleagues show that 25 percent of new drugs approved by FDA from 2008 to 2017 include a patent or other late-stage evidence of publicly funded research relating to an academic medical center or a spin-off company (Nayak et al., 2019). He added that this is appears to be a "notable increase" over prior decades.

- **Pricing and access via action under current laws.** This approach could make use of the Bayh-Dole Act provisions, such as march-in rights (discussed by Thomas earlier) and a nonexclusive royalty-free license for the government on grantees' patented inventions. One limitation is that, in many cases, "the fundamental contributions of NIH to drug development may not rise to the level of patent-

[54] The National Childhood Vaccine Injury Act of 1986 established a no-fault compensation system for individuals injured following vaccine administration. Funding is derived from an excise tax on the recommended childhood vaccines.

ing." Kesselheim said that retrospective strategies, such as march-in rights, are "suboptimal" and that march-in rights are in any case only applicable to a small number of drugs. In addition, as discussed by Stevens and others, march-in rights have never been exercised.

- **General drug pricing and access reform.** Kesselheim reiterated that drug prices in the United States are based on what the market will bear, not on drug development cost or a metric of value, and price negotiation by some government payers is prohibited. He said that the optimal legislative response would be to "allow the government to establish the clinical value of new drugs and effectively negotiate drug prices." He noted that there are models from other countries. He pointed out that if drugs were routinely accessible and affordable, and priced closer to the value they provide, there would be no need to consider drugs developed from NIH-funded research differently.
- **Safety net.** The "government patent use" provision, 28 U.S.C. Section 1498, allows the government to use patented inventions, and with the payment of "reasonable and entire compensation" that is set by the court. Kesselheim described this as an equivalent of eminent domain (Kapczynski and Kesselheim, 2016). For pharmaceuticals, "reasonable" could take into account a company's development costs, adjusted for risk of failure, to provide a reasonable profit, he said.

In closing, Tuckson called on panelists and participants to share any additional areas of research needed or strategies for ensuring affordable access. Sampat raised the idea of "direct and expanded public-sector funding of clinical trials and downstream product development" that could include stronger provisions for affordable access. Kesselheim said that NIH does invest in clinical trials to some extent and that public funding could take on a greater role in the later phases of development. He noted, however, that a private investment "has proven to be most effective" in the late phases. He suggested that public funders would need "to build capacity and expertise." Mitchell suggested that this approach could be applied to support the development of antibiotics that are urgently needed but for which profit is limited. Carino agreed that a role for government and philanthropy is to step in in areas of need where there is limited investment interest. A few participants also suggested other topics for future research and discussions including examining the quality of the training of the next generation of

clinical investigators, determining the value of a start-up biotechnology company, and addressing how investors decide whether and how much to invest.

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Appendix A

Statement of Task

An ad hoc committee will plan and host a 1.5-day public workshop to facilitate discussion focused on the translation of federal investments in biomedical science to innovation in drug development and how the public benefits from that investment in terms of drug pricing and access. The meeting will feature invited presentations and panel discussions on topics that may include:

- how federal funding for biomedical research, particularly via the National Institutes of Health (NIH), has contributed to new drug development, both directly and indirectly;
- the pricing of drugs that have benefited from federal investments in biomedical science;
- the role of technology and patent transfer to and from entrepreneurial organizations associated with NIH-funded research;
- potential ways to better track, quantify, and document NIH contributions to innovation in drug development; and
- potential strategies and policies to facilitate the translation of federally funded biomedical research into innovations in drug development and to help ensure that the public has affordable access to those innovative medicines.

The planning committee will develop the agenda, select and invite subject-matter experts and discussants, and moderate the discussions. A proceedings of the event will be prepared in accordance with institutional guidelines.

Appendix B

Workshop Agenda

WEDNESDAY, JULY 24, 2019

8:00 am **Registration**

8:45 am **Welcome and Workshop Overview**
Jeff Bingaman, J.D., Planning Committee Chair

9:00 am **SESSION 1: Keynote Address**
Moderator: Jeff Bingaman, J.D., Former U.S. Senator, New Mexico

Overview of the Translational Research Landscape
- Christopher Austin, M.D., National Center for Advancing Translational Sciences, National Institutes of Health (NIH)

Open Discussion

10:00 am **Break**

10:15 am **SESSION 2: Federal Funding for Biomedical Research and Its Contributions to New Drug Development and Commercialization**

Moderator: Amitabh Chandra, Ph.D., Harvard University

Session Objective: To discuss the impacts of publicly funded biomedical research and ways to better track, quantify, and document NIH investments that lead up to drug commercialization

Food and Drug Administration (FDA) Initiatives to Advance Drug Development Innovation

- Janet Woodcock, M.D., Center for Drug Evaluation and Research, FDA

The Public-Sector Role in Drug Development

- Bhaven Sampat, Ph.D., Columbia University

Gauging the Returns on Federally Funded Basic Research

- Danielle Li, Ph.D., Massachusetts Institute of Technology Sloan School of Management

Quantifying the Impact of NIH Funding on Pharmaceutical Innovation

- Margaret Blume Kohout, Ph.D., Gettysburg College

Panel Discussion

12:00 pm **Lunch Break**

1:00 pm **SESSION 3: Patent and Technology Transfer Policies in Promoting the Development and Commercialization of NIH-Conducted and -Funded Medical Research**

Moderator: Stephen Merrill, Ph.D., Senior Fellow and former executive director, Center for Innovation Policy at Duke Law

Session Objective: To discuss the current state of technology transfer agreements and licensing, and models for spurring drug innovation

Uncertainty About Patentable Subject Matter: Implications for Biomedical Research
- Arti Rai, J.D., Center for Innovation Policy at Duke Law

Technology Transfer at U.S. Academic Institutions Today
- Ashley Stevens, Ph.D., Focus IP Group, LLC

Reforming March-In Rights
- John Thomas, J.D., Georgetown University

Improving the Technology Transfer Process
- Chuck Na, M.S., National Institute of Standards and Technology

Panel Discussion

2:45 pm **Break**

3:00 pm **SESSION 4: Strategies and Policies to Facilitate the Translation of Federally Funded Biomedical Research into Drug Development and Commercialization**
Moderator: Jennifer Moore, Ph.D., R.N., Institute for Medicaid Innovation and University of Michigan Medical School

Session Objective: To examine ways to improve efficiency and lower the cost of clinical drug trials or other costly phases of drug development, and ways to incentivize translation of federally funded research discoveries into drug innovation

Clinical Trials: Risks and Costs in Drug Development
- Steven Galson, M.D., M.P.H., Amgen

Initiatives by the U.S. Department of Defense (DoD) to Advance Drug Development Innovation
- Terry Rauch, Ph.D., M.P.H., M.B.A., DoD

Collaborating to Accelerate Medical Product Development
- Lynn Hudson, Ph.D., Critical Path Institute

Strategies to Aid Repurposing of Compounds for Secondary Uses
- Christine Colvis, Ph.D., National Center for Advancing Translational Sciences, NIH

Infrastructure in Drug Development Innovation
- David Dilts, Ph.D., M.B.A., Vanderbilt University and Oregon Health & Science University

Panel Discussion

5:00 pm **Wrap-Up and Open Discussion**
Ameet Sarpatwari, Ph.D., J.D., Harvard Medical School and Brigham and Women's Hospital

5:30 pm **Adjourn Day 1**

THURSDAY, JULY 25, 2019

8:00 am **Registration**

8:30 am **SESSION 5: Drug Pricing and Innovative Financing and Business Models**
Moderator: Patricia Danzon, Ph.D., University of Pennsylvania

Session Objective: To discuss the economic implications of escalating drug costs and explore new ideas and opportunities, potential business models, and financing structures to accelerate drug discovery and development

Drug Pricing: The Components
- Patricia Danzon, Ph.D., University of Pennsylvania

Consumer Perspective on Recent Prescription Drug Price Trends
- Leigh Purvis, M.P.A., AARP Public Policy Institute

Innovative Drugs: Access to Medicaid Beneficiaries
- Doug Wirth, M.S.W., Amida Care

Innovative Financial and Business Models to Accelerate Drug Discovery and Development

- Kevin Outterson, LL.M., Boston University School of Law

Panel Discussion

10:15 am Break

10:30 am SESSION 6: Strategies and Policies to Ensure Affordable Access to Innovative Drugs That Have Benefited from Federal Investments

Moderator: Reed Tuckson, M.D., Tuckson Health Connections, LLC

Session Objective: To discuss new ideas and opportunities, and to explore potential public policies that should be implemented to ensure that the public has affordable access to innovative drugs that have benefited from federal investments

Taxpayer Funded Drugs and a Pricing Crisis

- David Mitchell, Patients for Affordable Drugs

New Ideas and Opportunities to Ensure That the Public Has Affordable Access to Innovative Drugs

- Tanisha Carino, Ph.D., FasterCures, Milken Institute

Potential Ways to Reform the Patent System to Ensure That Patients Have Affordable Access to Innovative Drugs

- Tahir Amin, LL.B., Dip. LP., Initiative for Medicines, Access & Knowledge, Inc.

Strategies and Policies Available to Bring About Transformative Reductions in the Increasing Prices of Drugs

- Aaron Kesselheim, M.D., J.D., M.P.H., Harvard Medical School and Brigham and Women's Hospital

Panel Discussion

12:30 pm Wrap-Up and Adjourn