Innovation in Drug Research and Development for Prevalent Chronic Diseases: Proceedings of a Workshop (2021)

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Innovation in Drug Research and Development for Prevalent Chronic Diseases

PROCEEDINGS OF A WORKSHOP

Andrew March, Amanda Wagner Gee, Robert Pool, and Carolyn Shore,
Rapporteurs

Forum on Drug Discovery, Development, and Translation

Board on Health Sciences Policy

Health and Medicine Division

The National Academies of
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Although the reviewers listed above provided many constructive comments and suggestions, they were not asked to endorse the content of the proceedings nor did they see the final draft before its release. The review of this proceedings was overseen by **BRADFORD GRAY,** Urban Institute (retired). He was responsible for making certain that an independent examination of this proceedings was carried out in accordance with standards of the 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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BOXES

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1

Introduction

Half of all Americans live with at least one chronic disease, such as heart disease, cancer, stroke, or diabetes. Chronic diseases—which are, broadly defined, health conditions that persist for 1 year or longer, that typically require ongoing medical attention, and that can interfere with the activities of daily living (CDC, 2021b)—are a major health concern in the United States and around the world. Chronic diseases are the leading cause of death and disability in the United States and are a leading driver of health care costs (CDC, 2021a).

Despite the human and financial costs of chronic diseases, investment in research and development (R&D) for the medical treatment of these conditions—other than cancer—has not kept pace with the rise in prevalence of chronic diseases in the American population. According to recent reports from the Congressional Budget Office and the Biotechnology Innovation Organization (BIO), a trade association that represents biotechnology companies and related organizations, venture investments (i.e., early stage funding) and innovation for drug development in several highly prevalent chronic diseases—depression, chronic pain conditions, addiction, type 2 diabetes, obesity, Alzheimer's disease (AD), and heart failure—have declined over the past decade relative to the prevalence and health care costs of these diseases (CBO, 2021; Thomas and Wessel, 2018a,b, 2019a,b, 2020). The recent outbreak of coronavirus disease 2019 (COVID-19) may further exacerbate the poor health outcomes associated with highly prevalent chronic diseases. A case series on hospitalized COVID-19 patients in the New York City area showed that the most common comorbidities were

hypertension, obesity, and diabetes—three examples of prevalent chronic diseases and conditions (Richardson et al., 2020).

On February 22, March 2, and March 8, 2021, the Forum on Drug Discovery, Development, and Translation (the Forum) of the National Academies of Sciences, Engineering, and Medicine (the National Academies) hosted a three-part public workshop[1] titled Innovation in Drug Research and Development for Prevalent Chronic Diseases. The workshop was designed to examine the unique cross-cutting challenges to increased investment in drug R&D for highly prevalent chronic diseases and to highlight opportunities to encourage innovation in this area. Specifically, the workshop's planning committee featured invited presentations and discussions in accordance with the Statement of Task (see Box 1-1). While non-pharmacological interventions—such as behavioral or environmental changes (Schmidt, 2016)—that can help treat and prevent prevalent chronic diseases also require additional research investment (IOM, 2011; NASEM, 2021), those interventions were beyond the scope of this workshop.

ORGANIZATION OF THE PROCEEDINGS

The organization of the proceedings groups the presentations of individual speakers into chapters according to the key themes that were discussed by workshop participants. Chapter 2 focuses on approaches for enabling more inclusive patient-centered clinical trial participation, and examines the value of incorporating patient input throughout the design and implementation of clinical trials. Chapter 3 explores practical and ethical considerations when using digital health technologies to better understand and treat prevalent chronic diseases. Chapter 4 examines some barriers to investment in drug R&D for certain prevalent chronic diseases, while Chapter 5 lays out some examples of success in drug R&D innovation for prevalent chronic diseases. Chapter 6 focuses on approaches and lessons learned that could be applied to improve and speed up the development of treatments for prevalent chronic diseases. Lastly, Chapter 7 recounts some of the major themes and points of emphasis that arose throughout the workshop discussions.

[1] This workshop was organized by an independent planning committee whose role was limited to the identification of topics and speakers. This Proceedings of a Workshop was prepared by the rapporteurs as a factual summary of the presentations and discussion that took place at the workshop. Statements, recommendations, and opinions expressed are those of individual presenters and participants and are not endorsed or verified by the National Academies of Sciences, Engineering, and Medicine, and they should not be construed as reflecting any group consensus. The workshop agenda and workshop speaker biographical sketches can be found in Appendixes A and B, respectively.

BOX 1-1
Statement of Task

A planning committee of the National Academies of Sciences, Engineering, and Medicine will organize and conduct a public workshop to examine the bottlenecks to innovation in drug research and development (R&D) for prevalent chronic diseases and highlight opportunities for spurring drug R&D in this space.

The public workshop will feature invited presentations and discussions to:

- Discuss the unique cross-cutting challenges to increased investment in early-stage research and late-stage drug development for prevalent chronic diseases (e.g., Do we have promising targets? Are the regulatory requirements predictable?);
- Consider whether investment and attention enablers are in alignment for spurring the type of R&D that will address unmet need when it comes to prevalent chronic diseases (e.g., Do we have the right business models in place?);
- Consider lessons learned from other disease areas (e.g., rare diseases) and/or use cases that could have cross-cutting applications for several prevalent chronic diseases; and
- Brainstorm and prioritize potential strategies to spur drug R&D innovation for several prevalent chronic diseases (i.e., highlight promising avenues forward that merit additional time/effort/funding/attention).

The planning committee will organize the workshop, develop the agenda, select and invite speakers and discussants, and moderate or identify moderators for the discussions. A proceedings of the presentations and discussions at the workshop will be prepared by a designated rapporteur in accordance with institutional guidelines.

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2

Person-Centered Drug Research and Development

Highlights*

- "Chronic disease wages war against every single dimension of wellness." (Veasley)
- It is vital to incorporate patient input throughout the design and implementation of clinical trials. (Winkfield).
- Diversity and inclusion in clinical trials should be considered in terms of race and ethnicity as well as geography and access. (Winkfield)
- "Community engagement is an essential piece in ensuring that we have better access to research for underserved populations and hope that this will help address health care disparities." (Woodahl)
- Stakeholders should consider how proposed research projects are of interest and have potential value to the people in the community. (Woodahl)
- Research that better serves underrepresented populations and improves equity will be "one of the most disruptive sets of innovations of the 21st century." (Mellad)

* This list is the rapporteurs' summary of points made by the individual speakers identified, and the statements have not been endorsed or verified by the National Academies of Sciences, Engineering, and Medicine. They are not intended to reflect a consensus among workshop participants.

A common theme throughout the workshop discussions was the importance of prioritizing the patient—patients' needs and preferences should be at the forefront throughout the drug R&D process. Christin Veasley, director of the Chronic Pain Research Alliance, emphasized the value of including the perspective of people who have lived experience with these conditions. Karen Winkfield, executive director of the Meharry-Vanderbilt Alliance, a strategic partnership between the Meharry Medical College and the Vanderbilt Medical Center, discussed ways to incorporate patient expertise throughout the design and implementation of clinical trials. Erica Woodahl from the University of Montana, who studies genetic variation in indigenous populations, provided insights on the barriers and opportunities for broader access to biomedical research for underserved and unstudied populations. Jason Mellad, chief executive officer (CEO) and founder of Start Codon—a UK-based accelerator, which offers funding to rapidly develop life science innovations—shared his thoughts on the promise of more equitable research.

CHRONIC PAIN: A PATIENT'S JOURNEY

According to a 2011 National Academies report, chronic pain afflicts 100 million Americans and is associated with more than $500 billion in direct medical treatment costs and lost productivity each year (IOM, 2011). Chronic pain conditions, which may result from various underlying diseases or conditions, share many attributes with other chronic conditions, said Veasley. Little information is available about the underlying biological mechanisms and causes of chronic pain, and animal models, translation, and research investment are insufficient, she explained. Few new drugs or other non-pharmacologics have been approved for the treatment of chronic pain. Although numerous therapies are on the market, data are insufficient to determine which treatments will be effective for which populations and which individuals. "And of course, our health care system is failing people with these conditions because we do not have team-based interdisciplinary care," concluded Veasley.

On a personal level, she said, capturing any one individual's experience is difficult. Veasley described the physical, emotional, spiritual, environmental, and vocational toll that one such disease—chronic pain—can take on individuals. She described living with a chronic disease as feeling like one is tethered to a ball and chain that grows heavier over time: In the beginning, a patient diagnosed with a chronic disease may feel upset, but motivated to find the right doctor, the right care, and a cure. Over time, the patient may see multiple doctors and try various treatments, while dealing with the long-term physical, psychological, and emotional burden

of the disease. As the burden of chronic disease grows heavier and heavier, it becomes harder and harder to move forward.

Veasley said the clinical trials enterprise is not designed to address the complexity of chronic conditions, particularly when it comes to issues related to comorbidity and multimorbidity. She pointed out that basic research tools (e.g., animal models) are not built to address questions about multimorbidity, and that clinical trials are often not adequately powered to assess disease heterogeneity and often exclude people with multiple chronic conditions. She added that disease classification is often based on signs and symptoms rather than the underlying mechanisms of disease. Lastly, payers frequently do not incentivize the type of interdisciplinary care needed to effectively treat people with chronic disease.

Veasley said the goal should shift from finding a cure to determining how to live well with a chronic condition. She concluded that this shift would require changing the entire system, not just addressing the issue disease by disease. This type of systems-level change would involve collaboration across different entities working as patient and advocacy organizations to examine each level of the drug R&D process to identify what needs to happen, determine who should take action, and how to incentivize that action.

THE IMPORTANCE OF THE PATIENT VOICE

Winkfield argued that a patient-centered approach to clinical trials is vital and offered suggestions for how to incorporate patients' input and expertise throughout the drug R&D process. She spoke about some lessons learned from her work in oncology and health equity that could be broadly applicable for other types of chronic illnesses. She expressed hope that researchers, regulators, clinicians, and patients can begin to think more critically about a patient-centered approach to the design and implementation of clinical trials.

When considering how to incorporate patient input before a concept for a trial has begun, Winkfield encouraged stakeholders to be mindful and creative. She acknowledged that this is not necessarily easy, but there are examples of success (see Box 2-1). The Wake Forest Comprehensive Cancer Center's Advocates for Research in Medicine (ARM) program was established as a mechanism for people with personal experience with cancer—survivors, caregivers, and individuals at high risk for cancer—to review research proposals and advise on clinical trials.

Winkfield stated that engaging patients means engaging patients from different communities—another area in need of improvement. A snapshot from the American Association for Cancer Research Cancer Disparities Progress Report shows that while differences in overall cancer death rates

BOX 2-1
Models for Incorporating Patients' Input in Research

The Wake Forest Comprehensive Cancer Center's Advocates for Research in Medicine (ARM) program. The purpose of the ARM program is to connect cancer patients and researchers to bring the patient perspective to research activities with the ultimate goal of improving outcomes (Wake Forest Baptist Health, n.d.). People with personal experience with cancer—patients, survivors, caregivers, and individuals at high risk for cancer—are matched with advocates and researchers. Participants are trained to work with researchers to advise, review, and implement clinical studies.

Community Engagement Studios, hosted by the Meharry-Vanderbilt Community Engaged Research Core. This program facilitates project-specific consultative meetings for patients and community members to provide input on research design, implementation, and dissemination (Joosten et al., 2015). For those interested in conducting similar engagement studies, the Community Engagement Studio Toolkit has been made available online at the Meharry-Vanderbilt Alliance website.[a]

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[a] https://www.meharry-vanderbilt.org//sites/vumc.org.meharry-vanderbilt/files/public_files/CESToolkit%202.0.pdf (accessed May 5, 2021).
SOURCE: Presented by Karen Winkfield, March 1, 2021.

between Black and White Americans are less pronounced today compared to 30 years ago, Black men and women continue to have the highest risk of cancer death (AACR, 2020). She pointed out that these health disparities apply across the board, including cardiovascular disease, diabetes, and HIV/AIDS, and are due in large part to disparities in access to care and the quality of care provided (NASEM, 2017).

While Winkfield recognized that part of the challenge in addressing these health disparities is that minorities tend to be underrepresented in clinical trials, she emphasized the need to hear from minority communities to better understand the underlying issues that lead to disparities in engagement in clinical trials. For example, a recent study published in *JAMA Oncology* showed that while 20 percent of multiple myeloma patients are Black, only 5 percent of people engaged in the clinical trials that were used to grant U.S. Food and Drug Administration (FDA) drug approval were Black (Loree et al., 2019). Winkfield emphasized the importance of access to and diversity in clinical trials in ensuring that drug developments benefit all communities. When designing trials, she asked stakeholders to consider whether a trial meets the needs of the intended patients affected by the dis-

ease, and whether the makeup of trial participants reflects the diversity of real-world populations. She reiterated the importance of engaging patients and their community early on in the research process and development of a trial.

In addition to considering racial and ethnic health disparities, Winkfield pointed out the need to consider the impact of geography on health disparities and access to clinical trials. For example, rural populations may have less access to clinical research sites and are often underrepresented in clinical trials. Additionally, individuals with fewer financial resources may be less likely to take part in clinical trials. She referenced the American Society of Clinical Oncology policy statement on addressing financial barriers to patient participation in clinical trials, which includes a number of recommendations concerning that issue.[1]

In closing, Winkfield highlighted a paper she and colleagues published in *JCO Oncology Practice* that offers an actionable framework to address cancer care disparities (Winkfield et al., 2021). Although the framework was developed for the oncology space, she suggested that many of the actionable items could be broadly applicable to other chronic diseases. She pointed to the importance of community engagement in the framework, saying, "You have to hear from your stakeholders in order to make a difference, in order to make sure that your clinical trials are meeting the needs of the populations you are trying to serve."

INCLUDING UNDERSERVED POPULATIONS

Woodahl provided insight on how to ensure broader access to biomedical research for underserved and unstudied populations. Her work is focused on indigenous populations, she said, but added that her observations should be generalizable to other underrepresented populations.

Woodahl's research is in the area of precision medicine and pharmacogenomics. As she explained, the goal of precision medicine is to identify variability among individuals in genes, environment, and lifestyle that can be useful in preventing and treating disease. In general, populations are heterogeneous, but medications are mainly delivered in a one-size-fits-all fashion, with a standard starting dose or regimen. However, not all patients respond to a medication in the same way: Some may not respond at all to the standard therapy, while others may experience adverse events when given a standard dose. One of the goals of pharmacogenetics is to better identify non-responders and individuals who are more likely to experience adverse events prior to initiating therapy.

[1] For more information, see https://ascopubs.org/doi/full/10.1200/JCO.18.01132 (accessed July 15, 2021).

Predicting the response of individuals to particular medications requires large-scale genetics studies, such as genome-wide association studies (GWASs). Despite dramatic growth in GWAS over the past decade and a half, Woodahl said, the majority of studies have been limited to populations of European descent (see Figure 2-1). The next two populations with the greatest inclusion in GWASs are individuals of East Asian descent and of South Asian descent. Far fewer individuals of African ancestry are included in GWASs, and indigenous people worldwide make up less than 0.02 percent of participation.

The lack of inclusivity in GWASs is a problem, Woodahl said, because it is unclear whether medical innovations coming out of these studies will be as useful for populations for which few data are available. Additionally, the availability of medical innovations is often limited to large academic medical centers, which are generally located in large urban areas. Populations living in rural areas may have comparatively less access to recent advances in precision medicine.

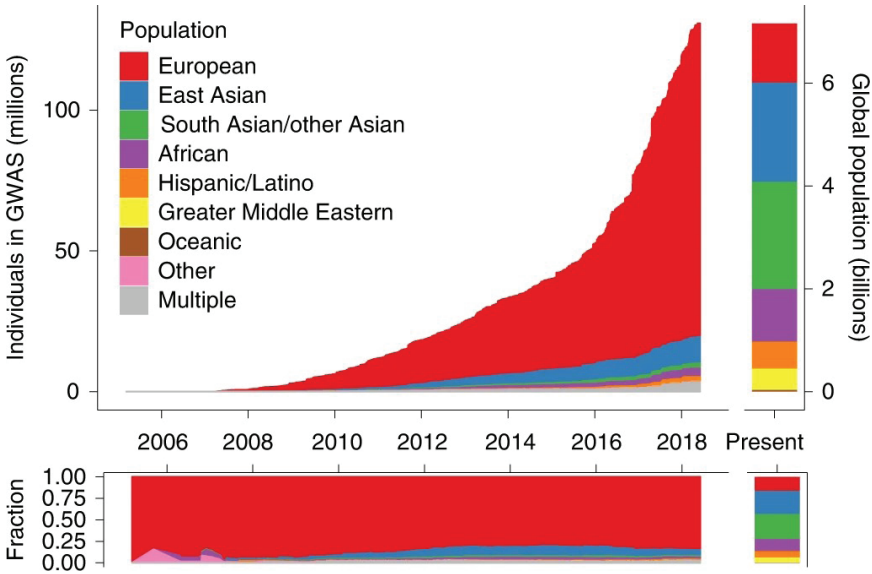

FIGURE 2-1 Genomics is failing on diversity.
NOTE: GWAS = genome-wide association study.
SOURCES: Presented by Erica Woodahl on February 22, 2021, at the Innovation in Drug Research and Development for Prevalent Chronic Diseases workshop; Martin et al., 2019.

Woodahl laid out a few of the barriers to increasing diversity in research:

- There is the perception that past research has provided little benefit to underrepresented groups. Woodahl referenced the term "helicopter research" to describe projects in which researchers go into a community to obtain samples and data, then leave and publish their papers. The community receives little direct benefit. Going forward, Woodahl asked stakeholders to consider how to address this issue, and ensure that proposed projects are of interest and have provided value to the people in the community participating in the research.
- Among minority populations, including American Indian and Alaskan Native communities, there is a lack of trust in the research enterprise. As an example, Woodahl pointed to a case in which researchers at Arizona State University had shared genetic samples collected for diabetes research with other researchers without the consent of the Havasupai Tribe.[2] The case led to backlash by indigenous communities against research. In 2002, the Navajo Nation put a moratorium on genetic research.[3]
- Concerns about data sharing and ownership can impede research efforts. The National Institutes of Health (NIH) requires data-sharing agreements when it issues genetic research grants, but Woodahl has worked with communities that were hesitant to relinquish control of their own data. She suggested that more flexibility is needed to accommodate diverse populations.
- A number of the communities that Woodahl works with are geographically distant from academic institutions, which requires investigators to travel large distances to reach community participants and build trusting relationships.
- Given issues with geographical remoteness, there may be a lack of laboratory infrastructure at community-based sites (e.g., it may be difficult to maintain the integrity of biological samples that must be transported from a clinical site back to an academic lab). Additionally, there may be a shortage of expert personnel at the community level.

[2] *Havasupai Tribe of the Havasupai Reservation v. Arizona Board of Regents and Therese Ann Markow*, 1 CA-CV 07-0454 and 1 CA-CV 07-0801 (Arizona Court of Appeals, 2009).

[3] Approving a Moratorium on Genetic Research Studies Conducted Within the Jurisdiction of the Navajo Nation Until Such Time That a Navajo Nation Human Research Code Has Been Amended by the Navajo Nation Council, HSSCAP-20-02 (2002).

Given these and many other considerations, communities may not be comfortable agreeing to participate in a research project without developing a clear understanding of the issues and having trust in the investigators. Woodahl relies on community engagement as a way to include diverse communities in her research. Her approach is to understand what communities considering participation in research want to engage in and how that research can be mutually beneficial to the researchers and the community as equal stakeholders. This approach requires that she build in sufficient time to develop relationships with community participants and sustain that partnership over time.

Woodahl is part of a community–academia partnership between the University of Montana and Native Americans belonging to the Confederated Salish and Kootenai Tribes. The partnership has carried out studies in cancer and cardiovascular pharmacogenomics, and currently has projects on the genetic and seasonal contributions to vitamin D sufficiency. A community advisory board meets with the researchers every month to talk about research progress, recruiting, new grant opportunities, and other relevant matters. The researchers have held genetic education workshops to provide opportunities for community advisory board members to learn about genetics and gain some hands-on training. Community advisory board members have been invited to visit Woodahl's lab at the University of Montana to see how the samples are stored and processed. She stressed the importance of this community engagement as core to her team's community-based participatory research model.

Woodahl shared some of the approaches she and her team have taken to recruit study participants. She described the importance of attending community events, such as pow wows and health fairs, as a way to recruit research participants. She noted that these approaches may be different from clinical research done in academic medical centers. For example, when she and her team drive out to the reservation they bring all of the supplies and equipment—portable freezers, centrifuges, blood collection supplies—that they need to recruit participants.

Woodahl recognized that the work involved is substantial, but said it is worth the effort to help ensure that medical innovations benefit all populations. More population-specific biorepositories are needed to advance research on chronic diseases. To build these resources, Woodahl suggested thinking outside of the box about ways to include underserved populations. "Community engagement is an essential piece in ensuring that we have better access to research for underserved populations and [we] hope that this will help address health care disparities," she said.

THE VALUE OF RESEARCH ON UNDERSERVED POPULATIONS

Looking to the future, Mellad said he believes research that better serves underrepresented populations and improves equity will be "one of the most disruptive sets of innovations of the 21st century." Minority populations are generally underrepresented in most clinical trials, he said. According to an FDA report, only 7 percent of patients in U.S. clinical drug trials from 2015 through 2019 were Black, compared with 13–14 percent in the general population (FDA, 2017). Ensuring that all populations are well represented needs to be a consideration beyond the clinical trial phase of drug R&D, he said. Including diverse samples must be a priority for preclinical work as well. "It is just not enough to find the individuals to be in your trial once you have a drug that is ready to go to market or diagnostic," he said. "You need to also be thinking about that when it comes to the biomarker discovery or therapeutic discovery upstream in the preclinical phase."

Mellad offered a brief description of a case study that illustrated a type of disparity that is often overlooked. Pulse oximeters are important devices for monitoring blood oxygen levels, which is particularly important for patients with diseases like chronic pulmonary obstructive disease or COVID-19. It turns out, he said, that the usual pulse oximeters may not provide accurate readings for individuals with darker skin tones (Sjoding et al., 2020). Given that Blacks are three times more likely to suffer a poor outcome from COVID-19, inaccurate, at-home pulse oximeters exacerbate the issue. The lesson, he said, is that it is not simply equal access to a technology or a drug that it is important; how the technology or drug was developed and whether it addresses the needs of the entirety of a diverse population is also crucial.

Getting access to populations that are underrepresented in clinical trials will be key to this work, Mellad said, and several companies trying to address this problem are getting interest from investors. The company Egality,[4] he noted, is working on the recruitment of patients for clinical trials to improve the representation of minority participants. The company Hurdle[5] is focused on managing patient care for underserved populations. By working with such companies, researchers will gain access to more patients from underrepresented populations, facilitating not only more representative populations for clinical trials, but also access to data that will help identify novel pathways. "The two go hand in hand," he said. "When I am looking for opportunities for investment, I am always thinking not only about the need that these companies are solving today, but also how can they pivot in the future when they build those informed consented databases of information, which will be valuable."

[4] See https://www.egality.health (accessed June 29, 2021).
[5] See https://www.startuphealth.com/hurdle (accessed June 29, 2021).

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3

New Technologies to Enable Research in Prevalent Chronic Disease

Highlights*

- Despite the vast amount of data generated and the availability of new analytical tools, scientific breakthroughs have been relatively limited for most prevalent chronic diseases. (Liu)
- Integrating multi-omics data, which broadly covers genome, epigenome, transcriptome, proteome, metabolome, and microbiome data, can be a powerful way to study complex diseases. (Liu)
- The application of new modalities for existing drugs has the potential to change the drug development paradigm for prevalent chronic diseases. (Colón)
- Integrating the use of digital health technologies and new modalities can improve the effectiveness of treatments for chronic diseases and give patients more control over their own health. (Colón)
- NIH's BRAIN Initiative is developing data and tools for understanding the brain that can serve as a foundation for basic discovery, leading to clinical research and, ultimately, clinical use. (Ngai)
- There is the need to democratize technologies and engage communities that traditionally have been underserved and underrepresented as true partners so that the work of the BRAIN Initiative can benefit all. (Ngai)

- Artificial intelligence applications have the potential to reduce time of development and increase the likelihood of success for early stage drug discovery. (Radin)
- Digital health technologies make it possible to collect many types of data remotely, and to collect data continuously and in real-world settings. These tools can help achieve broader participation and retention in clinical trials, and make it possible to find the right drug at the right time for a patient. (Kunkoski)

* This list is the rapporteurs' summary of points made by the individual speakers identified, and the statements have not been endorsed or verified by the National Academies of Sciences, Engineering, and Medicine. They are not intended to reflect a consensus among workshop participants.

The thoughtful integration of new and powerful emerging technologies, including digital health tools, artificial intelligence (AI) and machine learning, new modalities, throughout the drug R&D process offers opportunities to address critical barriers and streamline clinical trials for prevalent chronic diseases.

Qi Liu, senior science advisor in the Office of Clinical Pharmacology and Translational Sciences at FDA, offered her perspective on how innovations—new modalities, analytic tools, and new sources of data—that have enabled drug R&D and led to new treatment options for cancer patients could be applied to other chronic disease areas. Grace Colón, CEO of InCarda Therapeutics, provided three case studies that illustrated the value of thinking about technology in a more holistic way. John Ngai, director of NIH's Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative, discussed developing a collection of new tools for exploring and understanding the brain, many of which could be applied to prevalent chronic diseases involving the brain. Andrew Radin, co-founder and CEO of twoXAR Pharmaceuticals (renamed Aria Pharmaceuticals since the time of the workshop) spoke about AI applications to enable drug discovery for chronic diseases. Elizabeth Kunkoski, health science policy analyst with FDA's Office of Medical Policy clinical methodology team, offered a regulatory perspective on the development and use of health technologies in clinical research.

NEW INNOVATIONS IN DRUG DISCOVERY AND DEVELOPMENT

FDA focuses primarily on drug development and regulation, and does not play a major role in drug discovery. However, evaluating drug products has given Liu a unique perspective on how innovations in drug discovery

have led to new treatment options for improving public health. She shared a few examples from oncology that may offer applicable lessons for other prevalent chronic diseases. Liu categorized new innovations into three categories: (1) therapeutic modalities, (2) types of data, and (3) analytical tools.

New Therapeutic Modalities

Over the past decade, there has been significant growth in the development and use of targeted therapies, which Liu described as new molecular entities that are intended for a subset of patients who are identified through molecular testing. Biologics, particularly monoclonal antibodies, represent a fast-growing class of targeted therapy. As an example, Liu pointed to immune checkpoint inhibitors, which she said have been transformative in the treatment of patients with cancer and have become an increasingly important part of cancer treatment. She noted that James Allison and Tasuku Honjo won the 2018 Nobel Prize in Physiology or Medicine for their pioneering work in this field.

Liu also highlighted bispecific antibodies and antibody–drug conjugates as important innovations for the treatment of cancer. In 2009, only one antibody–drug conjugate had been approved by FDA (Joubert et al., 2020). In 2020, nine products have approval and several others are in the pipeline. The first FDA approval of a bispecific antibody came in 2014—blinatumomab was approved for use in the treatment of acute B cell lymphoblastic leukemia[1]—and many others are under clinical development.

Liu mentioned several other therapeutic modalities, including cell-based therapy, oligonucleotide-based therapy, microbiome-based therapy, and viral therapy. She emphasized that "today's breakthroughs in oncology are the result of decades of investment in cancer research and drug development." In 1971, President Nixon signed the National Cancer Act,[2] and in 2016, Congress passed the 21st Century Cures Act,[3] which authorized $1.8 billion in funding for the Cancer Moonshot[4] over 7 years. Industry has also invested heavily in oncology, which is now the largest pharmaceutical therapeutic area. Liu suggested a few reasons for this success: (1) basic research in cancer has led to a number of promising drug candidates; (2) there are strong financial incentives for investment; and (3) FDA's regulatory strategy for cancer drugs has been flexible and innovative.

[1] For more information on the FDA approval, see Mullard (2015).
[2] National Cancer Act of 1971, Public Law 92-218, 92nd Cong. (December 23, 1971).
[3] 21st Century Cures Act of 2016, Public Law 114-255, 114th Cong. (December 13, 2016).
[4] For more information, see https://www.cancer.gov/research/key-initiatives/moonshot-cancer-initiative (accessed July 16, 2021).

New Types of Data

Integrating multi-omics data, which broadly covers genome, epigenome, transcriptome, proteome, metabolome, and microbiome data, can be a powerful way to study complex diseases, said Liu. She highlighted a new type of -omics data, radiomics data, which she described as information extracted from medical images using algorithms. Radiomics has the potential to improve disease detection, characterization, and assessment, as well as prediction of treatment response.

Liu then discussed the opportunity and obligation to derive real-world evidence from real-world data[5]—information relating to patient health status and/or the delivery of health care routinely collected from a variety of sources including, but not limited to, electronic health records, claims and billing activities, product and disease registries, and patient-generated data—such as data from smartphones and wearables. She noted that in 2018, FDA issued a framework for the use of real-world evidence in regulatory decision making (FDA, 2018).

New Analytical Tools

Given the increased volume and types of data now available, Liu stated, "New analytical tools are needed to transform big data into smart decisions." She described a few examples of analytical tools that can play important roles in drug discovery and development:

- Model-informed drug development (MIDD),[6] which Liu described as the "application of exposure-based, biological, and/or statistical models, derived from preclinical and clinical data sources to address drug development and/or regulatory issues." She listed a few modeling approaches, such as physiologically-based pharmacokinetic models, quantitative systems pharmacology models, and quantitative structure–activity relationship models. As an example, Liu pointed to an application of MIDD to examine the in vitro antiviral activity of hydroxychloroquine to in vivo concentrations in order to predict how effective the drug might be in treating COVID-19 in humans. The study, which employed physiologically-based pharmacokinetic modeling and simulation, concluded that at normal doses, hydroxychloroquine was unlikely to achieve a high enough concentration to have an antiviral effect in humans

[5] For more information, see https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence (accessed July 16, 2021).

[6] For more information, see https://www.fda.gov/drugs/development-resources/model-informed-drug-development-pilot-program (accessed July 16, 2021).

(Fan et al., 2020). The paper was published in May 2020, and on June 15, FDA revoked its emergency use authorization for both hydroxychloroquine and chloroquine, referring to this MIDD analysis as one of the reasons for the decision (FDA, 2020a).

- AI and machine learning offer numerous applications for better understanding diseases and drug targets, generating and evaluating drug candidates and combination therapy, improving clinical trial design, and advancing precision medicine by improving diagnosis and treatment.[7] Liu shared a few examples of submissions with machine learning components received by FDA's Center for Drug Evaluation and Research, which included applications for predicting drug response based on baseline factors, identifying predicated biomarkers for drug response, and identifying drug abuse- related problems in postmarket settings.

Data sharing will be a key factor in encouraging innovation in prevalent chronic diseases, Liu said. Despite the vast amount of data generated, scientific breakthroughs have been relatively limited for most prevalent chronic diseases. The use of new analytic tools can help translate those data into smart decisions. "Investments from government and industry are needed for scientific breakthroughs. Data sharing and precompetitive collaboration can potentially benefit everyone, especially the patients. In the pursuit of innovation, if we want to go far, we need to go together," she said.

HOLISTIC APPROACHES TO INNOVATION

Colón offered three case studies illustrating ways innovation could be considered in a more holistic way, integrating various approaches in a value-based way to improve outcomes for patients: atrial fibrillation (AF), idiopathic pulmonary fibrosis (IPF), and chronic obstructive pulmonary disorder (COPD).

Atrial Fibrillation

AF, one of the most commonly diagnosed types of heart arrhythmias, impacts an estimated 6 million people in the United States alone (Morillo et al., 2017). It is a progressive chronic disease that is associated with increased morbidity and reduced quality of life in some patients. AF is esti-

[7] A more in-depth discussion on the applications of AI and machine learning in drug development is presented later in this chapter.

mated to cost the U.S. health care system more than $50 billion per year,[8] she said, if all expenses are included—therapeutics, health care usage, and invasive surgery.

The more a patient experiences AF, the more likely and the more extensive further episodes become. Yet, there is no good treatment option to stop an episode quickly, Colón explained. A number of antiarrhythmic drugs are available, but these have limitations: Some must be administered intravenously and others may take hours before they take effect. Some drugs taken orally are available for suppression, but may only work at high levels, so patient compliance is poor, and there are associated safety and tolerability issues.

InCarda Therapeutics is developing an inhaled version of a well-known drug, flecainide, which has the potential of stopping AF within a few minutes after an 8-minute inhalation.[9] The treatment is being studied in a medically supervised setting to verify flecainide response, but Colón suggested that if this medical product is approved for broader settings (e.g., work, home, travel), it could offer patients more options for determining their course of treatment. She added that the effectiveness of this intervention could be increased by combining it with the use of digital health technologies for disease monitoring. For example, a device that detects abnormal arrhythmia, coupled with confirmation from a patient's physician, could help facilitate increased awareness of AF and give the patient more control over their own health.

Idiopathic Pulmonary Fibrosis

IPF is a progressive, debilitating, and fatal lung disease. Although groundbreaking treatments have been approved in the past few years, most notably pirfenidone and nintedanib, these drugs have significant side effects, which can limit patient adherence. Colón pointed to the work of Avalyn Pharma, which is working on an inhaled version of pirfenidone.[10] Early studies in animal models have shown promising results, suggesting that small inhaled doses of pirfenidone can deliver therapeutic levels of the drug in lung tissue. Although the results are preliminary, she said this example "highlights the innovative use of an existing drug with a new modality to change the paradigm and potentially help these patients significantly with a much lower systemic dose and even improved compliance."

[8] The $50 billion figure is based on an estimate of $26 billion in 2004–2006, adjusted for inflation and an increase in prevalence. See Kim et al. (2011).

[9] For more information, see https://incardatherapeutics.com/2021/01/19/incarda-therapeutics-announces-enrollment-of-first-u-s-patient-in-phase-2-instant-trial-of-inrhythm-for-treatment-of-atrial-fibrillation (accessed July 16, 2021).

[10] For more information, see https://www.avalynpharma.com (accessed July 16, 2021).

Chronic Obstructive Pulmonary Disorder

COPD is a complex, multimodal disease associated with many comorbidities. There are no good single biomarkers that can help diagnose or manage COPD. Yet, diagnosis and management are important given that numerous triggers (e.g., viral infection, allergies) can lead to hospitalization. To address this gap, ProterixBio—of which Colón is the executive chair—has developed a disease activity score that uses an algorithm that takes into account a variety of inflammatory and immune response biomarkers measured against known patient populations.[11] Colón suggested that this approach has the potential to enable clinical trials for COPD and help physicians and health care systems better understand and monitor their patients over time.

Colón envisioned a future in which partnerships among different companies could integrate technologies for measurement, treatment, patient coaching, and interventions and apply these approaches toward prevalent chronic conditions, such as respiratory disease. New technologies offer opportunities to consider the overall patient journey and treatment paradigms, she said. Alternative routes of delivery and new modalities for existing drugs are two areas of promise. The use of novel biomarkers and integrating multiple biomarkers could lead to new endpoints and perhaps combination endpoints. These approaches could be integrated with digital health tools that provide better patient-reported outcomes and patient quality metrics. Holistic solutions "will require an integration of science, engineering, and medicine to address these problems together," Colón said. She concluded that these holistic approaches must take into account disparities in access to care and clinical trials by working to remove financial and transportation barriers so participants can enroll and stay in clinical trials.

THE NATIONAL INSTITUTES OF HEALTH BRAIN INITIATIVE

The BRAIN Initiative seeks to revolutionize the understanding of the human brain by accelerating the development and application of innovative technologies.[12] This collaborative public–private partnership includes federal agencies, private-sector companies, nonprofit organizations, foundations, and academic institutions. Ngai laid out seven key areas of focus for the initiative:

1. Discovering the diversity of cell types in the mammalian brains and other brains in order to "create a parts list";
2. Creating maps at multiple scales, or "wiring diagrams";

[11] For more information, see https://proterixbio.com/pipeline (accessed July 16, 2021).
[12] For more information, see https://braininitiative.nih.gov (accessed July 16, 2021).

3. Developing technology to monitor neural activity;
4. Developing technology to modulate neural activity;
5. Identifying fundamental principles in order to create a solid grounding for the work in theory and data;
6. Creating human brain research networks; and
7. Integrating the various approaches.

Ngai emphasized that the tools and resources developed by the BRAIN Initiative can serve as a foundation for basic discovery, leading to clinical research and, ultimately, clinical use. Work by the BRAIN Initiative is already helping to identify molecules, cells, and circuits affected in neurologic and neuropsychiatric disorders, he said, and pointing the way to interventions such as deep brain stimulators, sensory and motor neural prostheses, and targeted molecular and gene therapies.

Ngai suggested a few resources that could help support innovation in other fields, such as prevalent chronic diseases. For example, the BRAIN Initiative Cell Census Network[13] aims to create comprehensive brain cell atlases that integrate molecular analyses, connectivity, physiology, and other data for the mouse and other mammalian species, including humans and non-human primates. He suggested that the Cell Census Network may serve as a useful source of information for researchers seeking new cures for human brain disorders and other conditions.

The initiative already offers a large variety of resources that can be used in brain research. Ngai mentioned three brain cell data repositories: the Neuroscience Multi-Omic (NeMO) data archive for transcriptomic, epigenomic, and other omic information[14]; the Brain Image Library, with microscopy and other imaging information[15]; and the Distributed Archives for Neurophysiology Data Integration (DANDI), which offers neurophysiology information.[16] There are also repositories of analytical tools that allow the general research community to use the information from the data archives, including for disease-specific projects.[17]

Finally, Ngai spoke about the importance of carefully considering the ethical, legal, and societal implications for the work of the BRAIN Initiative. The Initiative's Neuroethics Working Group[18] has developed a set of neuroethics guiding principles, which deal with issues around safety and privacy as well as agency, malign, and dual use (Greely et al., 2018). Ultimately, he said, it is important to be mindful, responsive, and engaged with the public. He emphasized the need to make technologies more accessible to all people and engage communities that traditionally have been underserved and underrepresented as true partners so that the work of the BRAIN Initiative can benefit all.

Looking forward, Ngai said it has been challenging to find ways to share work generated from the BRAIN Initiative in ways that are broadly

accessible and useful to researchers, but there are efforts to make data more accessible to researchers, including those working in drug R&D. Additionally, he mentioned that the BRAIN Initiative is developing disease-agnostic tools that could be applied more generally to other disease areas. "What we are hoping to provide is a framework upon which we can hang the disease-specific projects," he said.

ARTIFICIAL INTELLIGENCE APPLICATIONS FOR DRUG DISCOVERY

While AI may seem new and exciting, Radin reminded workshop participants, this technology has been around for decades. In recent years, computing power and data storage have improved dramatically and been available at lower costs. Algorithms, such as deep learning and neural networks, have enabled more accurate predictions based on real-world data (e.g., weather predictions). Radin suggested thinking about AI as a tool one can use to predict an event using real-world data. Just as AI might be used to make weather predictions based on temperature, pressure, humidity, and cloud cover, this technology can be applied to many other domains, including drug discovery. Similar to weather prediction, Radin said, the process of finding a drug to treat a specific condition involves a number of uncertainties: Will the molecule reach the desired target in the body? Will the molecule interact with other targets that could lead to side effects? Does the animal model characterize well what will happen in a human? AI has potential applications for all of these questions and many more.

Radin's company, which is now known as Aria Pharmaceuticals, uses AI applications to identify candidate first-in-class small molecule treatments—drugs that use novel mechanisms of action—for complex diseases. There is an opportunity, Radin argued, to address unmet medical need by better understanding the biology of disease with the use of computational modeling systems.

As an example, Radin shared work the company has done on lupus, a disease that affects between 161,000 and 322,000 people in the United States (CDC, 2018). Given that lupus is an inflammatory disease, the typical initial treatment for lupus is the administration of non-steroidal anti-inflammatory drugs, which are safe, but not particularly effective for most lupus patients. Radin said many of the more effective drugs are also more toxic. For example, cyclophosphamide, which may be given to lupus patients with severe kidney inflammation, has a number of severe side effects, including infertility, birth defects, and blood clotting. He pointed to the need for a drug that is effective and well tolerated—likely a drug that has a different mechanism of action than drug treatments that are currently available.

Radin's company used AI applications to screen for small molecules with new mechanisms of action (see Figure 3-1). The first step, AI-driven discovery, was computationally intensive. The researchers characterized key biological features of lupus and built an in-silico model of the disease, based on 25 different orthogonal data sources (e.g., gene expression, protein expression, clinical data, and phenotypical data). These data were then processed by more than 60 methods to identify key features of the disease that could be mapped onto a small molecule library. Out of a small molecule library of 2 million compounds, 50,000 molecules were preliminarily screened as appropriate for the project, and the AI algorithm identified 3,000 molecules with the highest predicted efficacy out of that subset. Using AI-assisted review, researchers then screened the 3,000 molecules, examining the mechanism of action, safety profile, and other properties. This left 80 candidate molecules, which were then examined based on likelihood to be effective against the disease or have serious side effects. Intellectual property issues were also taken into consideration. This left nine molecules for testing in standard preclinical efficacy models. Radin said two of the molecules, TXR-711 and TXR-712, showed improvements in organ function and decreased inflammation in standard in vivo mouse models.

Radin highlighted the power of AI for advancing drug discovery. From project launch to the identification of nine candidate small molecules for screening took about 4 weeks. The preclinical testing took about 3 months. He pointed out that without the use of AI applications, this work could

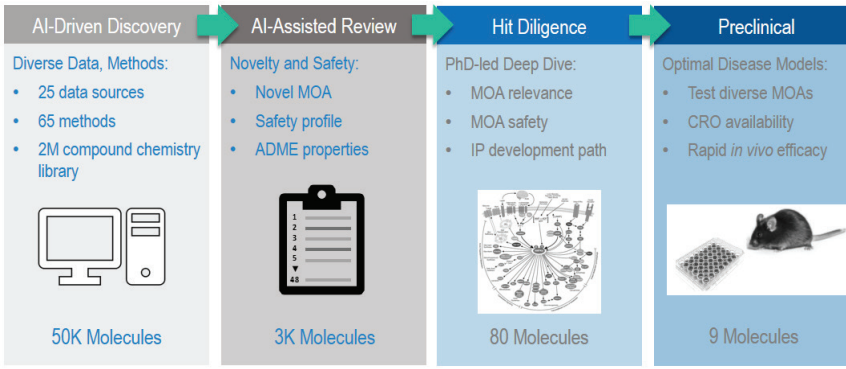

FIGURE 3-1 AI-assisted drug discovery.
NOTE: ADME = absorption, distribution, metabolism, and excretion; AI = artificial intelligence; CRO = contract research organization; IP = intellectual property; MOA = mechanism of action.
SOURCE: Presented by Andrew Radin on February 22, 2021 at the Innovation in Drug Research and Development for Prevalent Chronic Diseases workshop.

take years. He added that this approach was able to identify more candidate molecules than traditional approaches, which typically require far more in vivo testing to find one or two candidates.

Radin's company has had similar promising results across its portfolio of 18 diseases, including fibrotic diseases, immunoinflammatory conditions, and oncology. He emphasized that this work may not only lead to the discovery of new treatments, but it can also help the scientific community gain new insights into the biology of these disease areas.

A REGULATORY PERSPECTIVE ON NEW TECHNOLOGIES IN CLINICAL RESEARCH

Kunkoski offered a regulatory perspective on the use of digital health technologies in clinical research. Digital health technologies use computing platforms, connectivity, software, and sensors for health care and related uses (FDA, 2020b). Technologies include passive measuring devices, such as accelerometers, glucometers, and electrocardiograms, as well as more interactive tools, such as mobile phone apps and smart watches. She suggested that the possibilities for data collection through the use of digital health technologies are endless, and can make it possible to find the right drug at the right time for a patient.

One of the first steps for using a digital health technology in a clinical trial is verification and validation of the technology, which is intended to ensure that the data collected during the study are reliable. The verification step examines how accurate or precise the technology is in collecting data. In the case of an accelerometer, for instance, it might be important to assess how accurately it measures acceleration, if it is reliable in different environments, and whether readings are affected by the placement of the device. The validation step checks that the technology works as intended in the field when used by real people.

Speaking on the use of digital health technologies in clinical trials, Kunkoski listed a few potential applications. For example, digital tools could be used to remotely monitor a patient's response to a drug over a dosing cycle, which could be particularly relevant for chronic diseases. Capturing continuous or frequent measurements over time can provide valuable longitudinal information compared to cross-sectional data that clinicians might gather during a periodic clinic visit. "All of this means potentially fewer in-person visits for [research participants] enrolled in clinical trials," she said, "which means less time taking off of work, traveling less to research centers, which will enable more participation and greater retention in clinical trials."

For researchers planning to use a digital health technology in a clinical trial, Kunkoski said, the technology does not necessarily need to be approved by FDA or cleared for marketing. Instead, the main focus is

whether the technology can provide sufficient high-quality evidence for FDA to be able to draw conclusions about the safety and effectiveness of the therapeutic intervention being studied.

After verification and validation, another important step in preparing a digital health technology for use in a clinical trial is formulating an endpoint. The researcher must specify the clinical characteristic of the event being measured for each research participant and how the measurements will be used to assess the endpoint. Will that endpoint be, for instance, a single measurement such as blood pressure or the result of repeated measurements over a certain cycle, such as 24-hour ambulatory blood pressure monitoring? There can also be composite endpoints, she said, such as a combination of patient-reported outcomes and actigraphy measurements. Part of formulating the endpoint is determining the timeframe. Should it be steps in 1 hour? One day? One week? Or should it be a weekly progression over time? How should the response variable be reported—change from baseline, mean value, peak value, number of events, time to event?

Next, Kunkoski listed a number of factors that should be taken into account when selecting a digital health technology for a research study. The study population makes a difference, she said, observing that for many chronic diseases, there are elderly populations that may find it challenging to use the technology effectively. Other considerations include the study design, safety monitoring, technical support, and available training. "If you do not properly train the study personnel, investigators, and patients upfront," Kunkoski said, "you are not going to be able to get the data to make your trials successful."

As a case example, Kunkoski pointed to the use of digital health technologies with an accelerometer, gyroscope, and GPS to monitor how much a patient is moving after a hip replacement surgery (Bini et al., 2020). She suggested that the potential for real-time feedback may have the most promise given that this type of digital health technologies can provide the ability to engage patients in their recovery and allow them to track their own progress day by day.

Kunkoski reiterated that digital health technologies make it possible to collect many types of data remotely. They allow for broader participation and retention in clinical trials, and for more continuous data collection. "Now is the time for innovative thinking," she said. "We are excited about the potential for incorporating these technologies in clinical research moving forward."

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4

Investment and Incentives

Highlights*

- A confluence of factors is needed to spur drug development: a belief that a market for the intervention exists, a mechanism for reimbursement, regulatory flexibility, and governments willing to pay for those factors. (Axelsen, Schaeffer)
- Drug development decisions balance the cost versus the likely benefit of developing a particular drug for a particular disease, with the potential market size for the drug being a crucial factor. Given these parameters, the current system favors cancer drugs over cardiovascular disease, diabetes, and mental health interventions. (Axelsen)
- Innovation in drug R&D for AD has been limited, in part, due to the acceptance that the disease, similar to other chronic diseases, is just a part of the aging process, which has resulted in a lesser sense of urgency to find treatments. (Paulsen)
- Knowledge de-risks the development of new drugs and diagnostics, and investment follows, which has worked for some therapeutic areas. This has not been the case for prevalent chronic diseases. (Paulsen)
- A major trend in medical research that is of increasing interest to investors is personalized medicine. (Mellad)
- Research into the early detection of chronic diseases could offer promising investment opportunities. (Mellad)

- Early intervention can improve health outcomes and lower health care costs for prevalent chronic diseases. (Ehlert)

* This list is the rapporteurs' summary of points made by the individual speakers identified, and the statements have not been endorsed or verified by the National Academies of Sciences, Engineering, and Medicine. They are not intended to reflect a consensus among workshop participants.

Despite the significant public health impact due to prevalent chronic diseases, investment in drug R&D to treat these conditions—other than cancer—remains insufficient. Kirsten Axelsen, an independent consultant and visiting scholar at the American Enterprise Institute, offered a primer on the economics of drug development, with a focus on factors that influence investment decisions. Russ Paulsen, chief operating officer of UsAgainstAlzheimer's, described some of the investment challenges using AD as a case study. Jason Mellad, CEO and founder of Start Codon, an accelerator in the United Kingdom, offered some suggestions for overcoming resistance to investing in prevalent chronic diseases, including a focus on early detection and on underserved populations. Ken Ehlert, chief scientific officer of UnitedHealth Group, argued for the value of approaching the diagnosis and treatment of prevalent chronic diseases in ways that take individual patients into account.

To set the stage, Susan Schaeffer, president and CEO of the Patients' Academy for Research Advocacy, provided some context on funding and incentives for innovation in drug R&D for prevalent chronic diseases. She showed a figure illustrating the investigational products in drug development (see Figure 4-1). As shown, the largest percentage of products in development are for cancer (30 percent), while relatively small percentages of products are in development for indications encompassing most prevalent chronic diseases (neurology at 12 percent; autoimmune, would include rheumatoid and osteoarthritis, at 7 percent; endocrine/metabolic, would include programs for obesity and diabetes, at 6.4 percent; and cardiovascular indications at 3.8 percent).

Schaeffer listed a few reasons why relatively few drugs are in development for chronic diseases:

- A lack of biomarkers for measuring disease progression and measuring the progress in clinical trials;
- Inadequate animal models or other preclinical tools for interrogating the disease;
- A lack of sensitive endpoints that can be used to tell if the treatment is effective; and

- An inability to detect the disease at the earliest stages when it may be easier to intervene.

However, she noted there are a few cases in which interest and investment in the treatment of a chronic disease have suddenly increased. She mentioned two cases that could offer insights for boosting innovation for other chronic diseases: one case in which there was an increase in private investments in retinal diseases that took place in the mid-2000s, and a second case, which came a decade later, in which there was an increase in investments—mostly from new companies—working on hearing loss. Schaeffer described two factors that contributed to driving increased investment and attention.

First, biological discoveries opened up new targets and new pathways for intervention. In the case of ophthalmic disease, Schaeffer said, it was work with angiogenesis and vascular endothelial growth factor (VEGF), a protein that promotes the growth of new blood vessels. In hearing loss, the

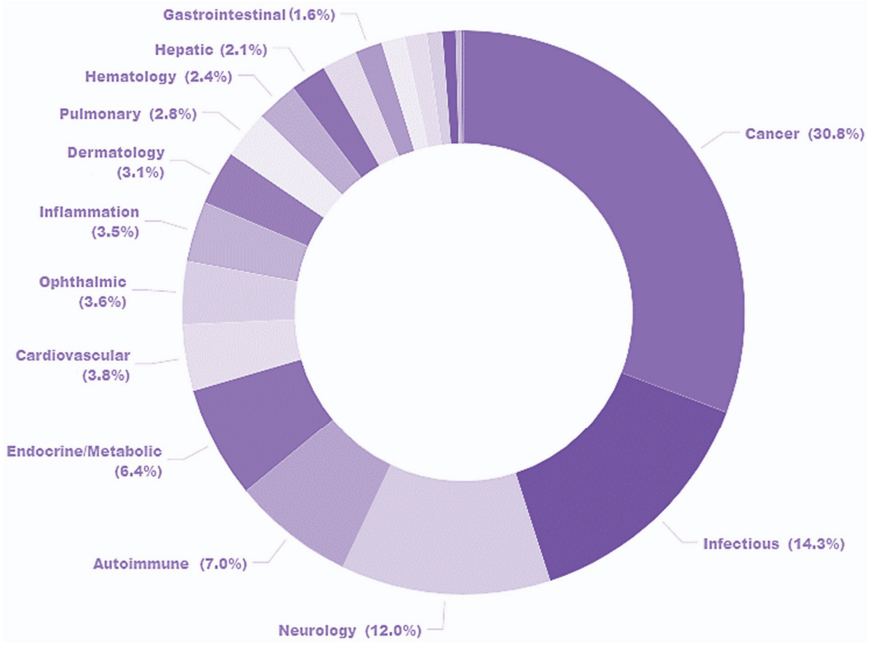

FIGURE 4-1 Drug, biologic, and vaccine candidates in preclinical development, clinical development, or registration.
SOURCES: Presented by Susan Schaeffer on February 22, 2021, at the Innovation in Drug Research and Development for Prevalent Chronic Diseases workshop; BioCentury's BCIQ database.

new discoveries centered on pathways related to the restoration of ribbon synapses for the regeneration of hair cells and drug delivery technologies that made it possible to deliver and retain drugs in the middle or inner ear.

Second, there were few treatment alternatives in these diseases so investors believed the return on investment would be favorable for new treatments in these areas. Conversely, Schaeffer said, if there is a belief that it will be difficult to get reimbursed for a new treatment, there tends to be less interest from venture capital firms supporting early-stage research or less interest from pharmaceutical companies in investing in later development, both of which can affect overall levels of basic research into the biologic basis of diseases. There is an opportunity to intervene at each of these stages of R&D and overcome the resistance to investment.

DRUG DEVELOPMENT ECONOMICS 101

Axelsen offered a broad view of the considerations that shape investment decisions for drug development. Fundamentally, she said, drug development decisions balance the cost versus the likely benefit—including improved outcomes for patients and return on investment for drug sponsors—of developing a particular drug for a particular disease, with the potential market size for the drug being a crucial factor. Additionally, low-income and minority populations, who are disproportionately affected by chronic diseases, tend to be undertreated and fewer resources are directed toward their health care. She recognized that the business calculations may be at odds with the burden of disease.

Axelsen laid out several factors contributing to increased costs for developing drugs to treat prevalent chronic diseases:

- There is a lack of investment in basic science for understanding the underlying biology of prevalent chronic diseases, which has limited genotyping for subpopulation prioritization and target identification for drug discovery.
- There is a lack of standardized metrics for environmental factors that contribute to chronic disease burden. Other than smoking and body mass index, few tools are available for incorporating environmental factors in clinical trials.
- Prevalent chronic diseases tend to have higher incidence rates among low-income and minority populations, who are more likely to receive care through primary care providers rather than specialists who may be more likely to identify and treat their specific conditions.
- Chronic disease patients often have multiple comorbidities, which add complexities to clinical trial design and implementation and further complicate patient treatment and care.

One area in which there has been some progress in finding treatments for chronic diseases is gene therapy, Axelsen said. For example, significant investment has been made in gene therapies for the treatment of hemophilia and sickle cell disease. However, she acknowledged that gene therapies tend to be expensive and the proliferation of high-cost therapies for multiple chronic conditions may not be sustainable for the health system.

A more practical approach may be to look to the broad array of low-cost therapies that are already available to treat chronic disease, such as statins and antihypertensive drugs. Even though generic drugs are available, poor adherence remains a problem. She suggested there may be value in more investment to understand the behavioral and financial incentives needed to encourage and support patient adherence.

In closing, Axelsen pointed to the rapid development of COVID-19 vaccines, which was spurred by a confluence of factors needed for rapid drug development: a belief that a market for the intervention exists, a mechanism for reimbursement, regulatory flexibility, and governments willing to pay for it.

CASE STUDY: ALZHEIMER'S DISEASE

Paulsen offered his perspective on funding for developing treatments for prevalent chronic diseases by discussing why it has been difficult to innovate in one particular chronic disease: AD. According to CDC, AD is the only disease among the top 10 causes of death for which there is no effective treatment. It affects about 5.8 million people in the United States today, and the rate is expected to roughly triple by 2060 (CDC, 2020). Costs for AD care make up a massive share of the Medicaid and Medicare budgets (Wong, 2020), he said. In short, there is a massive potential market for an effective AD treatment, Paulsen said. Yet, at the time of the workshop, a treatment for AD had not been approved in decades,[1] and a preventative drug has never been approved.

Barriers to Innovation in Drug Research and Development for Alzheimer's Disease

Paulsen suggested that one reason that innovation in drug R&D for AD has been limited is the acceptance that the disease, similar to other

[1] In June 2021, FDA approved the use of aducanumab for treatment of AD under the accelerated approval pathway. For more information, see https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/aducanumab-marketed-aduhelm-information (accessed July 15, 2021).

chronic diseases, is just a part of the aging process, which has resulted in less urgency to find treatments.

To gather better information and focus efforts, UsAgainstAlzheimer's, an advocacy and research-focused organization, asked AD patients what mattered to them about the disease.[2] What symptoms would they like to avoid? What abilities are most important to maintain? The results showed that AD patients cared most about outcomes associated with emotional well-being (e.g., not feeling depressed; not feeling like a burden to others). Many of the concerns raised by patients related to neuropsychiatric symptoms, which clinical researchers have not typically used as a primary endpoint in clinical trials.

Because AD is a neurodegenerative disease, there are no effective animal models. Furthermore, there are no simple, widely available biomarkers for AD, which makes it challenging to recruit and verifying eligibility of participants for clinical trials. Paulsen noted that positron emission tomography (PET) scans or lumbar punctures can reveal the underlying pathology of AD, but these tend to be expensive procedures and are not widely available.

Knowledge de-risks the development of new drugs and diagnostics, and investment follows, which has worked for some therapeutic areas, Paulsen said. However, for AD and other prevalent chronic diseases, limited understanding of the underlying biology and lack of good biomarkers have made it difficult to get funding at all stages of R&D. He noted that fewer than 1 in every 100 AD drugs that are tested actually succeed (Cummings et al., 2019), compared to the industry average, which is around 1 in 12 (DiMasi et al., 2016). The pool of resources is finite, and allocating those resources to disease areas like AD, which face underlying challenges throughout R&D, is a difficult decision to make, he said. Ultimately, he suggested, the solution may be for the U.S. government to step in with a program like the one it has for orphan drugs, encouraging investments in research.

AN INVESTOR PERSPECTIVE

Mellad shared his perspective as an investor in early-stage startups in therapeutics, diagnostics, and early detection. He observed that "If you look at the figures for the unmet need and the size of market for most chronic diseases, you would actually think on the surface, that it is an ideal space for us to be operating in." More than 55 percent of people over the age of 65 in the United States have two or more chronic diseases (CDC, 2015). Yet, with the exception of cancer, pharmaceutical companies and

[2] For more information, see https://www.usagainstalzheimers.org/press/new-usagainstalzheimers-research-shows-what-matters-most-patients-and-caregivers-drug (accessed July 19, 2021).

investors are not pursuing drug R&D programs that meet the needs of populations suffering from prevalent chronic diseases.

In looking for ways to fight disease, including chronic disease, Mellad pointed to the "innovation trinity" of early detection, prevention, and cure. Investment in the oncology space has clearly demonstrated the value of early detection – the earlier a cancer is detected, the easier it is to treat and the longer a patient is likely to survive (see Box 4-1).

Mellad acknowledged that risk aversion and bottlenecks associated with translational research—few research efforts actually translate into a clinical product—are widely recognized as barriers to innovation. Research programs fail for a variety of reasons, often related to unanticipated side effects, low tolerability of the drug, and so on, but Mellad said he believes many of these could be circumvented in ways that could encourage more investment in startups focused on innovative products.

One of the major trends Mellad sees is the shift toward personalized health care. Efforts to spur drug development for rare diseases have pio-

BOX 4-1
Prevention Can Be Profitable

Traditionally, Jason Mellad of Start Codon said, investors have been more interested in treatment because that was where the greater returns were, but the history of the company Exact Sciences[a] has shown that prevention can be profitable, too. Exact Sciences' development of ColoGuard, a home test to do early screening for colon cancer, has revolutionized the early detection of colorectal disease and potentially other gastrointestinal disorders, such as irritable bowel syndrome and inflammatory bowel disease. The company now has a market capitalization of $24 billion, which is attractive to investors. Increasingly, Mellad said, he is finding that investors are looking for other opportunities to invest in early detection and in biomarkers that can be used to identify novel pathways with which to treat patients.

Familial hypercholesterolemia is one example of a chronic disease that could offer a valuable investment opportunity in early detection, Mellad said. According to a recent report in *JAMA*, 1.3 million Americans suffer from that disorder, which puts them at a far greater than normal risk of heart disease, yet more than 90 percent have not been diagnosed (Knowles et al., 2017). If widespread screening for familial hypercholesterolemia took place, early interventions and a better stratification of patients when they go to the clinic for therapies could make a huge difference in the outcomes. But that would depend on carrying out research to find a useful biomarker and then developing a test. That is a funding opportunity.

[a] For more information, see https://www.exactsciences.com (accessed July 6, 2021).

neered this approach. The government played an important role by enacting the Orphan Drug Act, which provided incentives for innovations to treat rare diseases. There is now an infrastructure in place that can address narrower and narrower populations. Mellad suggested that this model could be applied to the chronic disease space. That said, investors would need to be convinced to back companies that can effectively fine-tune their approach to a narrowly defined population; payers would need to be willing to reimburse for a personalized therapy or diagnostic; and providers would need to be convinced that an intervention would work for a defined set of patients. As an example, he mentioned a company, Enhanc3D Genomics,[3] that has found ways to unlock the information in GWASs to identify novel druggable pathways for chronic diseases. "We are sitting on a treasure trove of novel genes and pathways that could be targeted to treat these disorders," he said. "I think that is going to engender a renaissance when it comes to new disease targets."

For diseases with established genetic and epigenetic underpinnings, such as familial hypercholerterolemia, widespread screening and early detection could enable earlier intervention and provide opportunity for improving the understanding of biomarkers, Mellad suggested. Additionally, these approaches could enable better stratification of disease subtypes, allowing for more effective treatments for patients. For example, Mellad proposed that early screening for familial hypercholesterolemia—a chronic disease that underpins cardiovascular disorders—could enable early intervention and better stratified patients when they present to the clinic for treatment.

A PAYER PERSPECTIVE

Ehlert used a single chronic diseases, obesity, as a case study to map out a philosophical approach to the development of drugs to diagnose and treat prevalent chronic diseases. Between 1990 and 2018, the percentage of the U.S. adult population that is obese grew from about 10 percent to 42.4 percent (CDC, 2021, n.d.), which presents a major strain on the health care system. Obesity can lead to a number of comorbidities, including diabetes, chronic kidney disease, and heart disease. Indeed, Ehlert said, as the baby boomer generation ages, statistics are showing a significant reduction in life expectancy, in large part related to chronic diseases (DuGoff et al., 2014).

When considering how to address prevalent chronic diseases, such as obesity, more effectively and at a lower cost, Ehlert agreed with other workshop speakers that early intervention is best to slow the progression of

[3] For more information, see http://enhanc3dgenomics.com (accessed June 29, 2021).

disease or prevent it altogether, sparing patients from the worst symptoms, and dramatically lowering associated health care costs.

Effectively diagnosing and treating a complex disease, such as obesity, and its related health effects requires understanding the disease on an individual level, which typically means having a reliable lab test or biomarker. For example, A1C, which is a test for blood glucose levels used to diagnose and monitor diabetes, could be useful for monitoring and treating obesity. However, Ehlert pointed out that lowering the blood glucose levels in individuals has not had great success in treating other chronic conditions associated with obesity, such as cardiovascular disease and kidney disease.

A better approach, Ehlert suggested, might be to study early biological effects and look for more appropriate biomarkers for early stages of disease that better capture disease complexity. Perhaps there are deeper, more fundamental factors that could serve as the basis for early-warning biomarkers—factors that could give an indication of early disease progression.

When considering approaches to cut costs and development time for drug R&D, Ehlert suggested that developers and other stakeholders in R&D move beyond thinking in terms of trying to treat 30 percent of the market with one therapy and instead find ways to treat segments of the population. For example, large pragmatic trials that include participants with comorbidities who are taking multiple medications, he said, could lead to a better clinical understanding at the time of marketing approval for how new treatments can best be used in individual patients. If researchers could find the right biomarkers to capture the different processes going on inside of individuals, he said, it may be possible to "radically alter how approvals happen, how clinical use gets adjudicated in the market, [and] whether or not a payer is actually willing to pay for it."

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5

Learning from Success

Highlights*

- Patient advocacy and philanthropic organizations can help to encourage the development of treatments for diseases by supporting early-stage research and reducing some of the investment risk for industry. (Coughlin)
- Digital health technologies hold promise in clinical settings for the management and treatment of chronic diseases. If used correctly, these digital health technologies can help streamline health care and make it more effective. (Abdulai)
- Many digital health technologies can be difficult for patients to navigate and use, which can limit their use. It is not always easy to determine which tools would be practical and applicable for individual patients. (Abdulai)
- Collaboration between government, academia, industry, and patient organizations can facilitate an understanding of unmet needs and speed the development of tools and treatments for chronic diseases. (Abdulai)
- Rather than taking the traditional approach of developing a new drug to treat one condition, a more efficient approach for drug R&D for prevalent chronic diseases might be to find one treatment that can apply to multiple diseases. (Heine)
- Designing and carrying out studies that are focused on total disease burden rather than on individual indications could

be made possible through the use of real-world evidence and pragmatic trials. (Heine)

* This list is the rapporteurs' summary of points made by the individual speakers identified, and the statements have not been endorsed or verified by the National Academies of Sciences, Engineering, and Medicine. They are not intended to reflect a consensus among workshop participants.

Workshop speakers offered success stories that provided lessons concerning what has worked and what has not in the fight against chronic diseases. Robert Coughlin, managing director of JLL's life sciences group and former president and CEO of MassBio, a Massachusetts biotech consortium, described how combined efforts from clinical researchers, hospitals, the biotech industry, and funders resulted in the development of a breakthrough drug to treat cystic fibrosis (CF). Raolat Abdulai, global clinical lead for immunology and inflammation at Sanofi, discussed how new digital technologies are playing a role in the understanding and treatment of chronic pulmonary obstructive disorder and other chronic diseases. Robert Heine, a distinguished Eli Lilly Scholar, called for a new way of thinking about the treatment of chronic diseases, one in which a single drug is used to affect multiple outcomes, with obesity and the metabolic syndrome as a case study.

CYSTIC FIBROSIS

Coughlin was 30 years old and running for the Massachusetts House of Representatives when he and his wife found out that the 21-week-old fetus his wife was carrying had CF. The amniocentesis test was still relatively new at the time, and they were one of the first couples in the country to be diagnosed with a baby in utero that was going to have CF. "We were basically told we were going to have a baby in several months that was going to have a disease for which there is no cure and the life expectancy isn't great."

Coughlin made a decision to continue to run for the House of Representatives to do what he could to encourage medical research "because government plays a major role in creating an environment so that people can cure disease and solve unmet medical needs." He also decided to work with the Cystic Fibrosis Foundation to raise money to invest in the innovation pipeline.

Getting involved with the Cystic Fibrosis Foundation was an eye-opening experience for him. Before that, he had assumed that doctors and scientists just cured diseases. He had not realized that it would take advo-

cacy, fundraising, and an average of 10 years and $1 billion—or more—to develop a new drug. His son, Bobby, was in six clinical trials before he was 6 years old. Coughlin learned firsthand how the system worked. "I realized the system wasn't very efficient," he said. "It didn't work very well. The drug discovery process was hard."

In 2007 Coughlin decided to leave the legislature and join MassBio,[1] a trade organization with a mission is to advance the life sciences sector in Massachusetts and improve patients' lives. At the same time, the Cystic Fibrosis Foundation was incentivizing a variety of biotech companies to do more research on CF by making early-stage research investments to limit the risk that these companies would otherwise face. The ultimate goal, he said, was to find drugs that, instead of treating the systems of the disease, changed the course of the disease by treating its underlying cause. One focus was gene therapy; another was precision medicine.

The results have paid off for people living with CF. In October 2019 FDA approved Trikafta for the treatment of CF in patients with a F508del mutation in the cystic fibrosis transmembrane conductor regulator (CFTR) gene; those patients represent about 90 percent of all people with CF (FDA, 2019). The drug, which is a combination of three individual molecules, works by helping the protein made by the CFTR gene function more effectively.

The breakthrough drug does not help everyone with CF, but, Coughlin said, it has made an amazing difference for his son. "He has gained 25 pounds, and his lung function has gone back up to 100 percent," he said. Although he recognized that there is still much work to be done in treating CF patients, Coughlin said he no longer has nightmares of his son dying before him.

Coughlin stated, "We're not just talking about drugs that treat symptoms of disease. We have drugs that change the course of disease by treating the underlying cause of the disease. We have gene therapy and precision medicine, some gene therapy that is actually curing disease now, and we don't have a health care system that can absorb those upfront costs." The early-stage investment by the Cystic Fibrosis Foundation helped reduce some of the risk for industry to develop much-needed therapies.

Coughlin emphasized the importance of advocacy. Advocacy groups raise money and awareness of a particular disease and the importance of addressing it. "If we don't go raise money and invest in our own early-stage research and identify mutations and help fund research moving forward, no one else is going to do it for our kids. I love doing it."

[1] For more information, see https://www.massbio.org (accessed June 29, 2021).

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Abdulai spoke about the use of digital health technology in the management of chronic diseases and also in clinical trials. If used correctly, digital health technology can help streamline health care and make it more effective, she said (Bashi et al., 2020; Morton et al., 2017). For example, diabetes can be monitored with the use of glucometers and different connected apps. Technology can also be used to manage the use of medications and monitor adherence. There are inhalers that make it possible to access whether a patient has been using them. Telemedicine is another example of using technology to manage chronic diseases. Since the COVID-19 pandemic started, Abdulai said, the number of patient visits carried out via telemedicine and telehealth applications has increased by a factor of 50 to 175, according to data from a recent report (Bestsennyy et al., 2020). Other uses of technology in chronic diseases include patient advocacy and community building, medical record management, and comorbidity monitoring and management.

If digital health technologies are to be used widely and successfully, Abdulai said, they must be able to meet specific patient needs. Chronic disease patients may have different comorbidities, be on different types of therapies, live in different environments, and have differing social determinants of health. Digital health technologies are also needed to accommodate different types of patient needs—medical, personal, emotional, and functional—as well as be able to engage patients, make patients feel self-efficacious in terms of their disease self-management, allow for effective communication between patients and providers, and increase overall accessibility.

With so many requirements, not all technologies are up to the task, she said. Many tools can be difficult for patients to navigate and use, which can limit their use. It is not always easy to determine which tools would be practical and applicable for individual patients. A resource that clinicians could use to help them evaluate these different tools would be beneficial, but an effective version does not currently exist, she said.

Moving from the clinic to industry, Abdulai said that biopharmaceutical companies are also using digital technologies in a large number of ways—in preclinical work, in data storage, and in the clinical/regulatory stage. She listed eight specific areas in which digital technologies are being used in the clinical research process:

1. Protocol design and review;
2. Site selection and startup;
3. Patient recruitment;
4. Operational management;

5. Drug and supply logistics;
6. The collection of digital biomarkers;
7. Patient and outcome data management; and
8. Conducting virtual trials.

Abdulai offered a case study of a digital technology designed to address an unmet need concerning physical activity in COPD patients, highlighting the role that collaboration among government, academia, industry, and patients can have in bringing treatments and technologies to market. COPD, the third leading cause of death in the United States, is a disease characterized by persistent limitation of airflow in the lungs, with symptoms that include chronic cough, sputum, and shortness of breath. Patients are often debilitated and limited in their activities because they are so short of breath, leading to a reduced quality of life. The cost of caring for COPD patients in 2020 was estimated at around $49 billion, she said (CDC, 2018).

The Physical Activity as a Crucial Patient-Reported Outcome in COPD (PROactive) project[2] was designed to more effectively assess physical activity and independence in COPD patients, and to better estimate the burden of disease. The project was carried out by the Innovative Medicines Initiative (IMI)[3] from 2009 to 2016.

In the case of the PROactive tool, whose development cost was more than $15 million, the objective was to develop a method to assess physical activity objectively using a validated activity monitor, combined with a set of questions, to capture the experience with physical activity in COPD patients. Abdulai emphasized the importance of making sure that digital technologies are well validated—and, in particular, health equity requires that the technology be validated across populations.

To do this, the development group first worked with patient groups to create a concept of how a COPD patient experiences physical activity. How does the patient experience walking outside, doing chores, doing leisure activities, dressing, bathing? What is their breathing like? Do they get fatigued? Do they have trouble with specific activities? Do they need to take breaks or slow down or get help from others? From the resulting conceptualization, the developers created a questionnaire tailored to the experiences of COPD patients.

They then integrated that questionnaire with two digital activity monitors, the Actigraph GT3X, which is worn around the wrist as a watch, and

[2] For more information, see https://www.imi.europa.eu/projects-results/project-factsheets/pro-active (accessed July 4, 2021).

[3] IMI is a European public–private partnership founded to improve health by speeding up the development of—and patient access to—innovative medicines in areas of unmet need (IMI, n.d.). It includes universities, research centers, the pharmaceutical and other industries, small and medium-size enterprises, patient organizations, and regulators.

the DynaPort MoveMonitor, which is worn around the waist. With those integrated activity monitors, the researchers created two patient-reported outcome tools for capturing physical activity, a daily measure of physical activity (Daily PROactive Physical Activity in COPD, D-PPAC) and a clinical visit measure that relied on a 7-day recall of activity (Clinical Visit PROactive Physical Activity in COPD, C-PPAC). By combining the responses on the questionnaires with the measurements of the digital monitoring devices, the resulting tool makes it possible to better understand the actual disease burden of reduced physical activity and physical functioning in COPD patients, Abdulai said.

The PROactive tool can be used in clinical trial settings to assess, for example, how well a drug for COPD is improving a patient's symptoms. This allows clinicians to move beyond simply assessing respiratory symptoms to see if a treatment is actually improving a particular patient's physical activity and functional status—measures of quality of life. In March 2018 the tool was adopted by the European Medicines Agency's Committee for Medicinal Products for Human Use (EMA, 2018).

In conclusion, Abdulai said digital health tools have an important role to play in the development of treatments, in clinical trials, and in health care. The development of the PROactive tool was the result of collaboration among multiple actors, including patients, to create a tool that incorporates both the traditional questionnaire and new digital tools, and that can now be used in clinical trials and beyond. She suggested that this approach to collaboration could be adopted in the United States to develop high-quality tools and treatments for prevalent chronic diseases.

INVESTING IN ONE DISEASE, APPLYING TO MULTIPLE DISEASES

The traditional approach to developing a new drug is to target one disease and test a drug against it, declaring success if it helps with that one disease. However, with so many patients experiencing comorbidities, Heine suggested that a more efficient approach might be to find one treatment that can apply to multiple diseases. In his talk he sketched out one way that might be done.

Heine discussed the obesity epidemic and the related health effects. In the United States, obesity rates have been growing since the 1970s, and it is projected that by 2030 about half of the U.S. population will be obese, that is, have a body mass index (BMI) greater than 30 (Ward et al., 2019). Estimates indicate that as many as 20 percent of all U.S. deaths are caused by obesity-related disorders (Masters et al., 2013).

Obesity and obesity-related diseases are also a growing problem in most of the rest of the world, Heine said. China is one compelling example. Average BMI has been increasing steadily, he said, and prevalence

of diabetes in China has risen to 120 million people (Chan et al., 2014). He noted that 25 percent of the global population of people with type 2 diabetes live in China. Furthermore, in just one decade the mortality rate for ischemic heart disease has quadrupled (Zhang et al., 2017), and about one-quarter of the adult population living in Shanghai are diagnosed with fatty liver (Fan et al., 2017).

Some causes of the obesity epidemic, he said, can be found in the abundance and easy availability of high-calorie foods—epitomized by fast foods—combined with a drop in average energy expenditure as people lead less active lives and use more labor-saving devices. The health implications have been deadly. Obesity leads to insulin resistance, hypertension, dyslipidemia, beta-cell dysfunction, fatty liver, and low-grade inflammation, leading in turn to a wide variety of diseases, including cardiovascular disease, hyperglycemia and diabetes, non-alcoholic steatohepatitis (NASH), cancer, chronic kidney disease, cognitive decline, and arthritis.

Metabolically, when a person becomes obese, the adipose tissue is no longer capable of taking up fatty acids and storing fat in a safe way, and the adipocytes become inflamed and start dying. Fatty acids are then stored in and around organs that are not equipped to store them, such as the liver or the heart. This in turn leads to high levels of lipids in the blood and the suite of disorders associated with metabolic syndrome—hypertension, type 2 diabetes, chronic kidney disease, atherosclerosis, and heart failure.

A standard way of identifying people at increased risk for these metabolic abnormalities is the defining characteristics of the metabolic syndrome. A person is diagnosed with metabolic syndrome when three or more of the following features are present: a large waist circumference (greater than 35 inches for women and 40 inches for men), elevated fasting glucose, elevated blood pressure (systolic greater than 130 or diastolic greater than 85), elevated serum triglycerides, and low levels of high-density lipoproteins (Huang, 2009). People with metabolic syndrome have a greater mortality risk, independent of obesity, and risk increases with an increasing number of metabolic syndrome features (see Figure 5-1).

The goal in treating obesity or weight gain-associated metabolic disorders, Heine said, should be "to reinstitute metabolic health, which can be defined as the absence of the metabolic syndrome components." Doing so should result in lowering the risk of developing multiple disorders related to metabolic syndrome. A therapeutic that improves overall metabolic health could also be evaluated for the treatment of specific metabolic conditions—cardiovascular disease, heart failure, diabetes, chronic kidney disease, NASH, and more—if the clinical endpoints are well defined.

One existing class of drugs has been shown to have effects on a number of these endpoints, Heine said: SGLT2 inhibitors, originally developed as glucose-lowering drugs to treat diabetes. The original clinical trial of

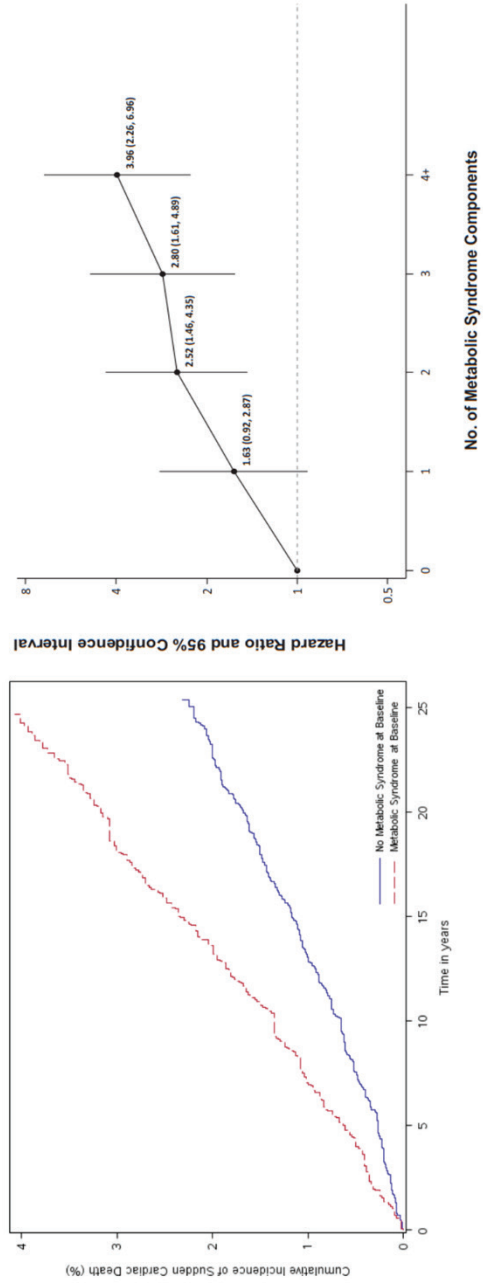

FIGURE 5-1 Increasing risk with increasing number of metabolic syndrome criteria.
SOURCES: Presented by Robert Heine on March 8, 2021, at the Innovation in Drug Research and Development for Prevalent Chronic Diseases workshop; Hess et al., 2017.

an SGLT2 inhibitor tested its cardiovascular safety, as required by FDA. Researchers found a reduction in cardiovascular disease outcomes with the SGLT2 inhibitor as compared with the placebo, which was mainly attributable to a reduction in heart failure (Sharma et al., 2020). Another trial demonstrated that SGLT2 inhibitors also reduce the risks of chronic kidney disease (Perkovic et al., 2019).

A new drug that helps obese patients to reliably lose weight could similarly hold promise against multiple aspects of the metabolic syndrome. For instance, Heine said, patients who have had bariatric surgery and lost a significant percentage of body weight have seen significantly improved outcomes in terms of mortality, cardiovascular disease, and microvascular disease (Doumouras et al., 2021). Weight loss of as little as 10 percent of body mass can result in a reduction of dyslipidemia, hypertension, hyperglycemia, insulin resistance, and fatty liver, improving metabolic health (CDC, 2020).

Recently, he said, several drugs—particularly the GLP-1 agonists—have produced weight loss that can render these major benefits (Trujillo et al., 2015). Thus, they offer a potential example of developing one treatment that can have positive effects on multiple diseases and outcomes. However, he discussed three major hurdles still facing successful R&D for obesity:

- Developing obesity drugs is expensive. Several companies have ceased R&D programs in the metabolic field because they did not see a practical way forward.
- Identifying the right patient for a particular therapy can be difficult. Not every person who is obese has a metabolic syndrome or is at the same risk as others with the metabolic syndrome.
- Many people do not consider obesity to be a disease, but rather a lifestyle problem. To move forward, it will be important to destigmatize obesity and gain acceptance of obesity as a disease and a major risk factor for multiple serious outcomes. Advocacy groups could potentially have a positive effect on this challenge, he said.

Heine suggested designing and carrying out studies that are focused more on total disease burden than on individual indications. For example, a single patient may be suffering from chronic kidney disease, cardiovascular disease, and diabetes, and clinical trials would ideally examine outcomes relevant to patients with comorbidities. This broader approach to drug R&D contrasts with the targeted approach on individual diseases that was suggested by Ehlert. However, both Heine and Ehlert stressed the need to understand the biology of the diseases being studied, including well-defined biomarkers and endpoints, in order to successfully evaluate the treatments being developed. Furthermore, Heine explained, as the experience with

bariatric surgery has demonstrated, it may be possible to use real-world evidence and pragmatic trials to demonstrate the effectiveness of some of these medicines. "This is a challenge," he said, "but also an invitation to everyone to start thinking about other ways to develop drugs for this metabolic disease that poses a huge challenge to the whole society."

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6

Lessons Learned for the Future

Highlights*

- Although the numbers of initial public offerings (IPOs) in the biopharmaceutical area have been growing, Rohrer said, and a record number—more than 100—of such companies went public in 2020, a large percentage of those IPOs were in the area of cancer, with relatively little investment in other chronic diseases. (Rohrer)
- There should be a focused research programs to address the early stages of chronic diseases to support therapeutics for prevention and the slowing of disease progression. (Rohrer)
- Managed care payers are reticent to pay for new drugs if generic classes of drugs are available, which contributes to the lack of innovation in drug R&D for prevalent chronic diseases. (Manolis)
- Successful new treatments for prevalent chronic diseases indicate there is a demand for more innovation in this area—mechanism of action, clinical materiality, and differentiation will always have a place. (Manolis)
- Public–private partnerships can spur innovation in drug R&D for prevalent chronic diseases by balancing risk and increasing the probability of success, especially in the realm of precompetitive research. (Menetski)

- The Foundation for the National Institutes of Health has funded a number of partnerships focused on better understanding drug targets and improving the operation of clinical trials, particularly through the validation of biomarkers. (Menetski)
- There is more openness on the part of regulatory agencies to consider new approaches in trial design than is often assumed. (Smith)
- Clinical researchers working on prevalent chronic diseases should consider innovative approaches for evidence generation (e.g., the use of master protocols, decentralized trials, and real-world evidence to inform medical product decision making). (Smith)

* This list is the rapporteurs' summary of points made by the individual speakers identified, and the statements have not been endorsed or verified by the National Academies of Sciences, Engineering, and Medicine. They are not intended to reflect a consensus among workshop participants.

Several speakers throughout the workshop looked to the future, focusing on approaches and lessons learned that could be applied to improve and speed the development of treatments for prevalent chronic diseases. Michelle Rohrer, global head of product development regulatory and policy at Roche, provided an industry perspective, offering a suite of suggestions to foster more innovative trial design and better incorporate patient input. Joseph Menetski, associate vice president of research partnerships at the Foundation for the National Institutes of Health, spoke about ways the foundation is helping to open up new possibilities for understanding and treating prevalent chronic diseases. Chronis Manolis, senior vice president of pharmacy at the University of Pittsburgh Medical Center (UPMC) Health Plan, discussed examples of success in innovative treatments for chronic diseases and how changes in reimbursement policies could encourage more innovation. James Smith, deputy director in the Division of Clinical Policy and Office of New Drugs at the Center for Drug Evaluation and Research at FDA, discussed some of the regulatory considerations and laid out a few opportunities for innovative trial design and data collection.

AN INDUSTRY PERSPECTIVE

Rohrer spoke from an industry perspective. Despite the availability of many promising innovations, clinical trials are currently taking longer and are more expensive to carry out than previously. A recent calculation indicated that new molecular entities cost an average of $2.6 billion to bring

to market, and the average success rate for developing new drug treatments is less than 12 percent (DiMasi et al., 2016).

Specifically, she described a few challenge areas that will be of particular importance in developing treatments for prevalent chronic diseases in the future:

- Trials are growing more complicated, with more procedures and more endpoints, with data from the Tufts Center for the Study of Drug Development indicating that between 2005 and 2020, the average number of data points for a phase III trial grew from 494,000 to 3.56 million (Tufts Center for the Study of Drug Development, 2021).
- There is a lack of investment in chronic diseases other than cancer. While there have been growing numbers of initial public offerings (IPOs) in the biopharmaceutical area, Rohrer said, and a record number—more than 100—of such companies went public in 2020, a large percentage of those IPOs were in the area of cancer, with relatively little investment in other chronic diseases.
- Although progress has been made toward community outreach and engagement with minority populations when recruiting for clinical trials, mistrust of the medical research community remains an ongoing barrier to carrying out clinical trials that include representative populations.

Turning from challenges, Rohrer then spoke of opportunities for research and development in the area of prevalent chronic diseases. The current environment is promising, she said, given that there is more investment in the biopharmaceutical industry than ever, even if not enough of that investment has yet been channeled toward prevalent chronic diseases. Furthermore, advances in digital health technology are opening up many opportunities. "There has never been a time when technology can so complement the therapeutic space," she said, mentioning as an example the stride velocity ankle bracelet, which is currently being validated to replace the burdensome 6-minute walk test. Additionally, the regulatory environment is more mature than ever before. More countries are joining the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use,[1] she said, "and we have regulatory flexibility that can also maintain high standards of quality, safety, and efficacy." The rapid response to the COVID-19 pandemic has provided an opportunity to implement new paradigms for drug R&D that can help bring treatments to patients faster.

[1] For more information, see https://www.ich.org (accessed July 16, 2021).

With those opportunities in mind, Rohrer discussed five specific areas that she suggested will be important for more effectively dealing with prevalent chronic diseases:

1. Collaborative investment in technology and biopharmaceuticals should be targeted for the treatment of prevalent chronic diseases.
2. There should be focused research programs to address the early stages of chronic diseases to support therapeutics for disease prevention and the slowing of disease progression. "Treating early is cost effective and has high impact on patients," Rohrer said. "But today, we have to admit that most of our therapeutics are being developed for late-stage disease."
3. In the case of COVID vaccines, companies were required to enroll diverse patient populations. Rohrer said, "It is incumbent on sponsors and regulators to not just keep running the same experiment and having the same result with 2 percent of our clinical trial population being diverse." Sponsors should recruit diverse participants to clinical trials and be held accountable for doing so.
4. There are many innovative approaches beyond randomized clinical trials that could be considered for regulatory decision making. These include model-informed drug development, adaptive clinical trials, Bayesian approaches, the inclusion of novel and digital endpoints, platform studies, testing multiple agents, the use of external controls, and the use of real-world data in assessing quality, safety, and efficacy. There may be resistance from regulators and investors, Rohrer acknowledged, but adopting new approaches will be crucial "because it is just not sustainable to insist on randomized clinical trials for absolutely every condition when we have these other perfectly valid innovative approaches to use."
5. "We must continue to partner with patients to further make sure their voice and concerns are front and center in our clinical trial and regulatory decision-making forums," she said. With telemedicine and other digital health technologies, patients can participate in one or more aspects of trials without having to step foot in a clinical site. Rohrer added that researchers should consult with patients on whether particular trial designs are workable for them or if the endpoints are truly meaningful in assessing their quality of life.

"This is a huge burden on our society as well as our families and individuals whom we love," she said in conclusion, "and if we can put rovers on Mars, we certainly can do better for patients with chronic disease."

A PAYER PERSPECTIVE

Speaking from a payer's perspective, Manolis offered his own perspective on how best to mobilize the R&D research engine to deal with prevalent chronic disease. He began with the observation that the pharmaceutical industry is currently facing unprecedented levels of complexity due to a number of factors: transformative drugs, the impact of digital health technologies, drug pricing, industry consolidation, the regulatory environment, and the evolution of values. Any one of these factors alone could create a daunting environment, Manolis said, but all of them together "creates one of the more challenging environments I have seen in my 30 years in this business."

Specialty drugs, which include most injectable drugs, biologics, and other medications that require special administration or ongoing clinical assessment, account for nearly 38 percent of all spending on retail drugs, even though only 5 percent of the population uses a specialty drug (Hill et al., 2020). This is reflected in the drug pipeline which, again, shows a disproportionate emphasis on rare diseases, cancer, and neurologic disorders—with the traditional chronic diseases very much underrepresented (see Figure 6-1). Indeed, Manolis said, for years clinicians have been relying on generic classes of drugs to treat conditions such as hypertension, mental health, high cholesterol levels, and peptic ulcers, and there has been little

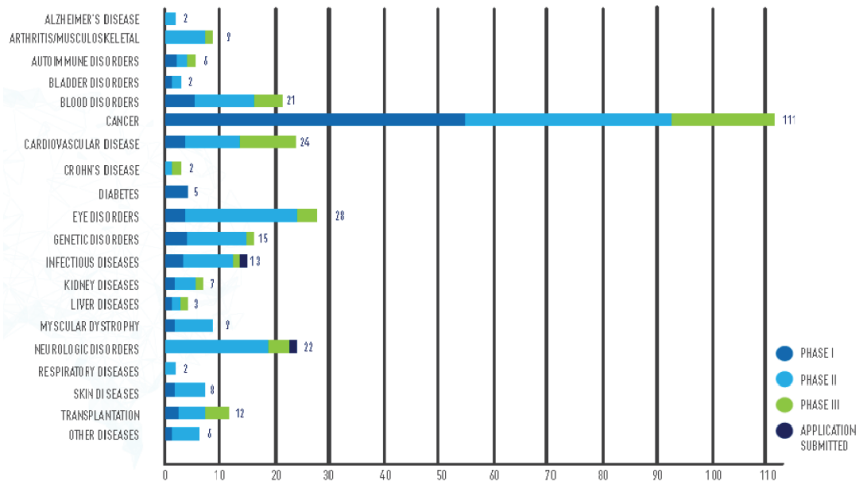

FIGURE 6-1 Cell and gene therapy drugs in the pipeline.
SOURCES: Presented by Chronis Manolis on March 1, 2021, at the Innovation in Drug Research and Development for Prevalent Chronic Diseases Workshop; Pharmaceutical Research Manufacturers of America, 2020.

innovation in these areas. Managed care payers are reluctant to pay for new drugs for these conditions, which contributes to the lack of innovation, Manolis said. This, in turn, impacts whether a company might be willing to support research programs for prevalent chronic diseases.

Another issue is what Manolis called the "pharmacy benefit managers rebate machine"—the current practice of pharmaceutical companies paying rebates to pharmacy benefit managers to favor their drugs, which can skew the choice of drugs put on a formulary.

Nonetheless, Manolis continued, there have been some recent innovation successes in dealing with prevalent chronic diseases. SGLT2 inhibitors and GLP-1 agonists have proven valuable in treating diabetes (Nauck and Meier, 2005; Whalen et al., 2015). Direct-acting oral anticoagulants have proven effective in treating and preventing blood clots and now account for more than 97 percent of the individuals in the UPMC Health Plan Medicare program who are on blood thinners (Chen et al., 2020). Similarly, a number of new products are now available to treat migraines (Han et al., 2019), and are replacing triptans, which were the standard of care for years. In short, he said, it is clear that there is room for innovation even in the prevalent chronic disease space.

Furthermore, he said, there is no question that payers will get behind innovation and that deserving drugs will be accepted onto formularies so that payers will reimburse for them. "I can tell you as someone who leads a $4 billion pharmacy operation, mechanism of action, clinical materiality, and differentiation—they always have a place," he said. "They will always get a look, and it is all about the data." Ultimately, he added, payers are focused on the total cost of care (see Box 6-1).

One approach for encouraging innovation will be to take advantage of increasing demand for new, more targeted and more effective drug therapies. The numbers of physicians in accountable care organizations—in which compensation is tied to the quality of care and reductions in cost of care—is rapidly increasing, and these physicians, Manolis said, are particularly interested in new differentiated therapies that can be matched to individual patients. Those patients, if they are educated and engaged, may demand new and better treatments. The key, Manolis said, will be in harnessing this demand to encourage more innovation in drug R&D for prevalent chronic disease.

A PUBLIC–PRIVATE PARTNERSHIP PERSPECTIVE

The Foundation for the NIH is an independent, not-for-profit organization that was established by Congress to support the mission of NIH. Menetski highlighted two Foundation for the NIH partnerships: the

BOX 6-1
Minimizing the Total Cost of Care

The University of Pittsburgh Medical Center designs its benefits to minimize the total cost of care, Manolis said. For example, in accordance with the center's Medicare diabetes drug policy, all of its diabetes drugs for Medicare patients have been moved to the generic tier. Type 2 diabetes patients typically have multiple comorbidities and may have trouble affording their drugs, so the medical center's decision was to help ensure its members could afford these diabetes drugs and provide education on how to take the drugs, with the expectation that the center would save money down the line.

"It has been a real success story so far," he said, but it has also been a challenge. Many people questioned the strategy, wondering why the medical center would want to attract diabetics to its Medicare program by making their drugs so inexpensive. But, Manolis said, the center's calculation was that with the drug treatments available today, as long as the patients would take the drugs as prescribed, the end result would be a reduction in the total cost of care.

Accelerating Medicines Partnership (AMP)[2] and the Biomarkers Consortium.[3] Each of these partnerships has focused on precompetitive research with implications for drug development. The foundation will typically require a partnership to include at least three private partners and two research institutions. The expectation is that the field will benefit from the knowledge generated by these partnerships.

The Accelerating Medicines Partnership

AMP launched in 2014 as a public–private partnership among NIH, FDA, multiple biopharmaceutical and life science companies, nonprofits, and other organizations to transform the current model for developing new diagnostics and treatments

Based on input from NIH director Francis Collins and representatives from biopharmaceutical companies, AMP has focused on identification of drug targets. In particular, Menetski said, AMP focused on making sure that targets that had been identified in animal models translated to humans. Initially, AMP started such programs on type 2 diabetes, AD, rheumatoid arthritis, and systemic lupus erythematosus. These initial programs have

[2] For more information, see https://fnih.org/our-programs/AMP (accessed June 29, 2021).
[3] For more information, see https://fnih.org/our-programs/biomarkers-consortium (accessed June 29, 2021).

since been joined by several others, including programs on Parkinson's disease and schizophrenia, with others under development.

The teams developing the programs include members from "industry, patient groups, NIH, academia, pretty much anybody that had a stake in that space," Menetski said, with each member having input on the plan going forward. That was important, he said, because success depended on industry and NIH support. The projects are designed with milestones and go/no-go decision points.

Menetski shared a couple of examples of success:

- AMP—rheumatoid arthritis, systemic lupus erythematosus.[4] This project focuses on understanding the immunological underpinnings of the disease at the individual cellular level, and has defined standards for collecting tissue, isolating cells, collecting data from multi-omics platforms, and analyzing the data. For both diseases, Menetski said, research teams identified a number of cell types that have a strong pathologic effect on the disease—not only the usual suspects, but a number of new low-prevalence cell types as well. This type of work could not have been done by any one company, he said, and it was even tricky for NIH to carry out.
- AMP—AD[5] and type 2 diabetes.[6] AMP's work on AD generated a set of new targets by standardizing the collaborative analysis of large datasets from multiple different cohorts. The project on type 2 diabetes produced a publicly available repository of genetic data to help researchers identify genes of interest and validate drug targets.

The Biomarkers Consortium

The Biomarkers Consortium, by contrast, has focused on generating drug development tools that can be used to enhance the results from clinical trials. Janet Woodcock, acting commissioner of FDA, commented that although thousands of papers are published each year on biomarkers, few of them are useful for clinical decisions. There are generally too few data to be confident about a decision and too much ambiguity. Especially given the current emphasis on precision medicine, it is important, Menetski said, to develop better tools for clinicians to assess factors such as who is sick

[4] For more information, see https://fnih.org/our-programs/AMP/amp-ra-sle (accessed July 16, 2021).

[5] For more information, see https://www.fnih.org/our-programs/amp-alzheimers-disease-phase-2 (accessed July 16, 2021).

[6] For more information, see https://fnih.org/our-programs/AMP/accelerating-medicines-partnership-type-2-diabetes-project (accessed July 16, 2021).

with what disorder, what the future outcome is likely to be for that person, what drug would work best, and whether a given therapy is producing the expected results. Biomarkers can play a role in all of these areas as well as in drug development and testing.

The approach of the Biomarkers Consortium is similar to that of the AMP, Menetski said. Over its 14 years of operation, the consortium has started more than 30 projects. He added that an important contribution of the Biomarkers Consortium, in addition to biomarker identification, has been in advancing a promising idea to a definitive tool in the regulatory context.

As an example, Menetski pointed to the Osteoarthritis Biomarkers Project.[7] Osteoarthritis is a highly prevalent disease, but available therapies only provide symptomatic relief. Traditional measures of disease progression and response to treatment were limited and the existing research base was small. Before the consortium got involved, there had been some initial work on biomarkers, but none could be confidently used in the clinic. The consortium team, which includes companies looking for disease-modifying therapies and academic research leaders, has since identified several new biomarkers for predicting disease progression and treatment response in clinical trials, which were submitted to FDA's Biomarker Qualification Program.[8]

Menetski emphasized the value of public–private partnerships in spurring innovation in drug R&D for prevalent chronic diseases. Collaboration enables risk sharing and can increase the probability of success.

A REGULATORY PERSPECTIVE

Smith highlighted the heterogeneity of chronic diseases from a drug development perspective, stating that, "with respect to available therapies, some disorders have hardly any truly effective available therapies, whereas others have multiple classes, sometimes with substantial availability of generic products." He recognized there could be variability across chronic diseases in terms of the pathophysiology and how well the underlying disease biology is understood, and in terms of the degree of regulatory precedent with respect to suitable endpoints for clinical trials. On top of these considerations, Smith suggested that in many cases, drug R&D for prevalent chronic diseases may require large clinical trials to detect the treatment effect or ensure an adequate safety database, particularly if existing safe and available therapies are available.

[7] For more information, see https://fnih.org/our-programs/biomarkers-consortium/osteoarthritis-project (accessed July 16, 2021).

[8] For more information, see https://www.fda.gov/drugs/drug-development-tool-ddt-qualification-programs/biomarker-qualification-program (accessed July 16, 2021).

Smith offered a few thoughts from the perspective of evidence generation. For example, in response to the COVID-19 pandemic, the use of master protocols have offered a faster path to treatment and could be applicable for other therapeutic areas, including prevalent chronic diseases. Smith suggested that there is more openness within FDA to consider new approaches to trial design than is often assumed, and he challenged the clinical research community to "push the envelope a little bit." As an example, he mentioned a meeting of the Cardiovascular and Renal Drugs Advisory Committee in which the Division of Cardiology and Nephrology expressed an interest in using "graded adjudication" to judge cardiovascular events. In graded adjudication, he explained, instead of adjudicators making a binary, yes/no decision concerning whether an outcome event has occurred, potential negative events could be assigned a likelihood of probability. "We have been doing cardiovascular outcome trials for decades," he said, "and there might be ways to innovate here that would actually provide more outcome events" and thus improve the efficiency of the trial.

The implementation of decentralized clinical trials, in which some or all trial-related procedures and data acquisition take place at locations remote from the investigator, could also offer new opportunities to reach patient populations who might not otherwise be included in clinical trials.

Another opportunity, Smith suggested, could be leveraging real-world data—information collected through clinical practice (e.g., data acquired from electronic health records, medical claims data, or other such sources) to support regulatory decision making.[9] He mentioned in particular that FDA's guidance for conducting trials during the COVID-19 pandemic noted that it may be necessary to collect safety and efficacy assessments in alternative ways, such as through virtual assessments.

Finally, Smith said it is important to consider which data are absolutely necessary to collect in a trial. Clinical researchers often collect a number of data points on large numbers of patients, which can significantly increase the cost of a trial. "Certainly, patient safety is paramount in clinical trials," he said. "I would not want to suggest otherwise. But it is fairly typical for us to see protocols that include comprehensive safety data collection regardless of the stage of drug development—even after approval—with the collection of voluminous laboratory data and EKGs and physical exams and non-serious adverse events." He suggested that there could be opportunities for stakeholders to reconsider what information is relevant and actionable, and then scale back on some data collection while still accomplishing the goals of the trial and meeting the needs of regulators.

[9] For more information on the role of real-world evidence in medical product development, see NASEM (2019).

Smith stated that FDA remains interested in collaborating with stakeholders to develop new ways to formulate drugs for prevalent chronic diseases effectively and efficiently. He recognized that FDA has not yet seen the data from most COVID-19 trials, but expressed optimism that lessons learned from these trials could and should be applied to answer clinical questions and improve clinical trials for other treatments in the future.

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7

Reflections and Final Thoughts

Highlights*

- Developing treatments for prevalent chronic diseases will require broad systemic collaborations and incentives that align across patient and research communities. (Colón, Schaeffer)
- Patients, caregivers, and advocacy groups should be integrated throughout the drug R&D process for prevalent chronic diseases. (Colón, Drake, Schaeffer)
- Including diverse populations is crucial throughout the research process, from basic exploratory research to clinical trials. (Schaeffer)
- The dramatic increases in volume and type of biomedical data open up new avenues for drug development but also pose a variety of challenges, such as how to handle and analyze the data effectively while ensuring patient privacy. (Colón, Drake, Rosen, Schaeffer)
- Chronic diseases are best addressed through early detection and intervention. (Drake)
- "Clinical trials are becoming increasingly complex, but there is room for innovation in the way they are conducted and analyzed that is acceptable not just to regulators, but also to community members and patients." (Drake)
- New innovative technologies, such as AI, can play an important role in improving the development of therapies for prevalent chronic diseases. (Rosen, Schaeffer)

- In the development and testing of therapies, endpoints should consider input from patients and caregivers. (Colón, Drake)

* This list is the rapporteurs' summary of points made by the individual speakers identified, and the statements have not been endorsed or verified by the National Academies of Sciences, Engineering, and Medicine. They are not intended to reflect a consensus among workshop participants.

The workshop concluded with reflections and consideration of next steps for spurring innovation in drug R&D for prevalent chronic diseases. Anantha Shekhar from the University of Pittsburgh and Carlos Garner from Eli Lilly and Company moderated a panel discussion in which Susan Schaeffer, Bettina Drake of Washington University School of Medicine, Howard Rosen from BonVelo Ventures, and Grace Colón summarized workshop key themes and highlighted some of the cross-cutting strategies discussed over the course of the workshop.

ENGAGING PATIENTS THROUGHOUT THE RESEARCH PROCESS

Schaeffer recognized that "knowledge gaps that are discouraging investment in R&D for prevalent chronic diseases are far too big for any one company or institution to fill." Instead, developing treatments for prevalent chronic diseases will require broad systemic collaborations to reduce cost and risk. Several speakers had proposed establishing an Operation Warp Speed for prevalent chronic diseases to jump start innovation and accelerate progress.

Patients must be an integral part of such collaborations, Schaeffer stated. Any time that a development process does not include representation from the patients who are the expected beneficiaries of that process, "we miss out" because the process does not include relevant information about the patient experience and what patients need from new medicines. The lack of information and understanding, in turn, increases development risks and limits the potential benefits of the treatment for patients. Colón added that motivating patients and their caregivers is crucial, but challenging, because there has been so much frustration and failure relative to the potential treatments for many prevalent chronic diseases. She said that patients are savvy about what to expect from a new drug or therapy, and will be drawn to the promise of real innovation.

Drake emphasized the importance of engaging patients and incorporating their input throughout the research life cycle, including early-stage study design. By working with patients and community members in clinical trials, she added, researcher have an opportunity to build trust. Particularly at

large research centers, she said, there is no lack of patients who are passionate about their condition and want to help the next generation, their family members, or society in general, so there is no excuse for not including patient voices throughout the R&D process. For example, Schaeffer added, if basic research studies are carried out using material from biorepositories that are biased toward individuals of European descent, clinical studies farther downstream in the development process may yield drug products that do not work as well in other populations or have differential toxicity effects. For this reason, it is crucial to include diverse populations throughout the research process—from basic exploratory research to clinical trials.

Schaeffer emphasized that physician engagement, particularly among community physicians, is also important. This is especially relevant when it comes to certain chronic diseases that may lead to stigma and blame placed on patients with such conditions, she said. For example, obese patients with severe osteoarthritis may be told that the solution for their pain is to lose weight even if they have already made dietary changes and their osteoarthritis makes it difficult for them to exercise. "We need to engage physicians," Schaeffer said, "and we need to break through this cultural idea that these conditions are either inevitable, unfixable, or due to poor lifestyle choices or poor patient decisions and characterize this as a research question that needs to be invested in and a series of conditions that actually we can improve."

The good news, Schaeffer said, is that patient advocacy organizations and community-based organizations can help establish more patient-oriented research priorities. As an example, she referred to Russ Paulson's presentation in the first workshop session in which he described how UsAgainstAlzheimer's went out into the community to talk to individuals living with AD and their caregivers about what is important to them. What they learned from this work was that patient concerns did not align with typical primary outcome assessments for AD clinical trials. Similarly, Christin Veasley from the Chronic Pain Research Alliance described what is important to chronic pain patients. The chronic pain is only part of it, Schaeffer said. It can lead to problems such as brain fog, depression, fear, and sleeplessness, but these problems are not necessarily captured in a numerical, visual, analog scale for pain. She reiterated Veasley's point that by communicating what is most important to patients—patient advocacy organizations—can help establish research priorities and identify where new tools and more knowledge are needed.

Another way that patient advocacy organizations can help tackle research issues, she said, is by helping to organize and fund collaborations aimed at answering some of the big questions about prevalent chronic diseases. They can help with recruiting patients when researchers are ready to begin clinical trials and with the dissemination of research results in

ways that are understandable and meaningful to the individuals who are most affected by a particular chronic disease. Schaeffer stated, "We need to ensure that incentives are aligned for both the patient communities and the research communities to collaborate together in partnership to answer these questions and break through barriers to innovation in R&D for prevalent chronic diseases."

In closing, Schaeffer repeated a comment she had heard from Heather Gainsworth, a researcher from The University of British Columbia who has worked to develop a set of guiding principles for collaborations between individuals with spinal cord injury and researchers working to understand and treat such injuries. Gainsworth said she often hears from researchers that they would like to engage with patients, they understand that it is important, and they even believe it is the right thing to do, but it takes time. What Gainsworth tells the researchers, Schaeffer said, is that if their goal is to produce publications, then yes, it takes longer to communicate with patients. However, if their goal is to generate knowledge that can be translated into patient care that improves lives and improves outcomes, then it is actually faster to work with patients.

CONSIDERATIONS FOR DESIGNING CLINICAL TRIALS

A major theme cutting across several of the workshop sessions, Drake said, was the importance of a patient-centered approach in designing clinical trials. The conclusion by Karen Winkfield, executive director of the Meharry-Vanderbilt Alliance, was that patients and community members should be included at every stage of the process. "By doing this," Drake said, "you not only build trust, but you are able to incorporate feedback all along the process." One consideration is how best to include patients and caregivers during the early stages of drug research and development. There are opportunities to include patients in early research decisions, Drake said: They can advise on a research concept, they can review proposals and provide feedback, and they can communicate with the broader communities about the value and impact of basic and clinical research.

Another theme that arose from the workshop sessions, Drake said, is the value of early intervention, which can improve patient outcomes. She emphasized the need to focus on what is most important to patients and caregivers and seek therapeutic interventions that improve their quality of life. To this end, it is crucial to seek patient input about what results matter most to them.

Some of the workshop discussions examined how changes in clinical trials triggered by the COVID-19 pandemic may affect R&D practices in the future. A number of lessons can be applied, Drake said. For example, she noted, "We are much more comfortable with e-consenting, much more

comfortable with allowing participants to enter data or collect data in their homes or doing self-sample collection kits or entering data online, which could help us reach a broader audience moving forward."

With increasing use of digital technologies in decentralized trials, Drake noted that there are a number of new and emerging technologies for real-world data collection. For example, mobile devices can track physical activity or heart rate throughout the course of daily life. With this ability, she emphasized that there is a need for researchers to deliberately choose which specific data would be useful in a clinical trial in advance and make plans for collecting and analyzing this information.

Drake observed that "Clinical trials are becoming increasingly complex, but there is room for innovation in the way they are conducted and analyzed that is acceptable not just to regulators, but also to community members and patients."

Given that many patients experiencing chronic disease suffer from more than one disease at a time, a holistic approach that accounts for individual variability can help capture important effects of candidate treatments, said Colón. Drake added that comorbidities may vary across different populations, underscoring the importance of capturing variability in clinical trials. Colón acknowledged that including diverse populations in trials introduces new challenges. "We need to be more creative about how to design these trials with new statistical approaches so that we can include all of these populations with enough statistical power," she said, "but also be able to do subanalyses and understand how a particular treatment or particular overall pathway is impacting these various populations."

Schaeffer said there is an openness among regulators to approaches that involve comorbidities. One example is FDA's guidance on including patients with brain metastases in cancer clinical trials.[1] The guidance proposes an option to include patients without brain metastases for the clinical trial's primary endpoint, but simultaneously include patients with brain metastases for secondary, subpopulation-specific analyses.

NEW TECHNOLOGIES AND INNOVATIVE APPROACHES

Given the many uncertainties associated with the progression of chronic diseases, the use of artificial intelligence could play a useful role in unravelling the mysteries of pathogenesis and analyze large volumes and types of data, said Rosen. As John Ngai explained in his remarks, NIH's BRAIN Initiative is generating large amounts of data, as are a variety of other programs, which can be analyzed using AI approaches to inform drug discov-

[1] For more information, see https://www.fda.gov/media/121317/download (accessed July 16, 2021).

ery and development programs. Interestingly, Rosen observed, data from diverse sources can strengthen algorithmic predictions. Schaeffer added that real-world evidence could help reduce the risks typically associated with drug development for prevalent chronic diseases.

Along with the potential, there are also a number of challenges, Rosen noted. Analyzing large amounts of data raises a variety of process questions, such as determining the best ways to format and share the data. What sort of formats will be accessible to the greatest number of data users? How can people be made aware of the data and given easy access to it? Large datasets containing data taken from individuals also raise a number of privacy-related challenges. These are magnified when the data are collected from small populations, such as members of indigenous populations, as noted by Erica Woodahl from the University of Montana. Schaeffer emphasized that data-heavy approaches require thoughtful consideration of patient data protection, data ownership, and governance to ensure that information is handled in an ethically responsible and equitable manner.

Overall, Rosen concluded, the workshop left him optimistic about the potential for formulating new techniques to speed the drug development process and having an impact on prevalent chronic diseases.

LESSONS LEARNED

Colón summarized examples of past success that could offer lessons learned for innovation in drug R&D for prevalent chronic diseases going forward. Chronic diseases are complex and multifactorial, so a single drug or device is never enough, she said.

Robert Coughlin of JLL spoke passionately about a success story from CF, and Colón emphasized the power of passionate patient advocacy groups to push research forward. However, she cautioned that people do not always have the time and resources to advocate or lobby. She noted that this can be an even a greater challenge for underserved populations.

Colón highlighted the importance of pushing for endpoints that reflect patient preferences and quality of life. She highlighted the IMI project on COPD,[2] which led to the development of patient-reported outcome tools now in use. Those tools are particularly important, Colón remarked, because COPD is complex and patients with COPD often have comorbidities.

The integration of patient-facing digital health tools in trials for chronic disease management, as raised by Raolat Abdulai, holds promise. Such

[2] For more information on the IMI PROactive project, see https://www.imi.europa.eu/projects-results/project-factsheets/pro-active (accessed July 3, 2021).

integration requires taking a holistic look at what patients want and need, from managing their own care to carrying on in their daily lives. Engaging caregivers and allowing patients to achieve self-management should be a goal for chronic disease management, she said.

For complex diseases that affect multiple organ systems, Colón emphasized the promise of a cross-functional approach. Robert Heine, an Eli Lilly Scholar, gave an example of metabolic syndrome and its associated disorders. The syndrome is particularly worrisome because it is growing not only in the United States but globally as well, and it leads to many other comorbidities. Colón emphasized the promise in focusing on total disease burden rather than on any one endpoint. She added that because metabolic syndrome has many different implications, it is important to look at real-world evidence and understand what is happening in patients' lives in order to understand the types of innovations that will be most valuable.

The good news, Colón said, is that a variety of companies are looking to put innovative technologies to work in every aspect of clinical trials, from risk mitigation to novel biomarkers and composite endpoints, "and so there is a lot of optimism about the future."

Potential Opportunities for the Future

The panelists proposed a few areas in which investment and attention could spur innovation in drug R&D for prevalent chronic diseases:

- There are opportunities to rethink the overall patient journey and to develop new treatment paradigms enabled by new technologies and approaches, including modalities and routes of delivery, the optimization of formulations and device combinations, novel biomarkers, and digital health technologies. (Colón)
- Underserved populations are disproportionately affected by prevalent chronic diseases, so increased focus on the inclusion of patient and community voices across the entire R&D life cycle is needed. (Colón, Drake)
- Success in dealing with prevalent chronic diseases will require new levels of collaboration and sharing among all stakeholders: patients and advocacy groups; federal, state, and local governments; regulators; venture philanthropy; academia; the biopharmaceutical industry; payers and providers; technology developers; and more. "This is a call to action for all of us to work together on this." (Colón)
- Leveraging public resources to address complex conditions that drive illness, and supporting collaborative initiatives to diagnose and treat early-stage prevalent chronic disease, can improve quality of life and long-term outcomes. (Colón, Drake, Rosen)

- It is important that payer incentives and health economics are aligned because secondary and tertiary costs of these diseases are often not factored into cost calculations. (Colón)
- Conducting outreach efforts supported by industry, educating patients about drug R&D, and engaging patients and communities as partners can provide valuable knowledge to improve drug R&D for prevalent chronic diseases. (Schaeffer)
- Defining and validating novel endpoints for clinical trials can help reduce the overall cost of prevalent chronic disease clinical trials and improve the relevance of studies for patients, clinicians, and payers. (Colón)
- There are opportunities for increased use by sponsors and support by regulators for using adaptive trial designs and novel data sources, such as real-world data, in rigorous analyses. (Colón)
- Private investors and venture philanthropists have opportunities to invest in companies developing novel approaches aimed at unmet medical needs. (Colón)

Ensuring that patients have access to care should be a top priority because it enables the early detection of chronic diseases and comorbidities, said Colón. Health insurance policies can also play a major role, said Rosen. Many Americans spend time without health insurance, which makes it less likely that their chronic diseases will be detected and addressed early. Rosen suggested that targeted policy changes could help improve patient access to and use of health care. Drake noted that it is important to ensure that policy changes are implemented well and that individuals take advantage of them. For example, even though Operation Warp Speed was successful in developing several COVID-19 vaccines, the vaccine rollout and uptake varied across the country. Similarly, even if insurance policies are put in place, individuals still need to enroll in the insurance programs and take advantage of the policies.

Robert Califf from Duke University and Verily Life Sciences said that economic issues are going to be an important factor in the nation's response to prevalent chronic diseases. The U.S. government made major commitments and upfront payments that took away some of the risks for COVID-19 vaccine development for industry, but he added that this cannot be done for every disease. Economic incentives will likely play a role in spurring innovation in drug R&D for prevalent chronic diseases, he said, but it will take considerable policy discussions for how best to proceed. Colón suggested examination of the regulatory and reimbursement changes made in response to the pandemic to learn what might work for the longer term.

In closing, Garner pointed to the transparent and open dialogue among leaders, FDA, and industry as well as the shared sense of urgency that

characterized the nation's response to COVID-19 as a positive example of collaboration. He suggested that prevalent chronic diseases could benefit from applying that same transparent communication and sense of urgency to address the nation's most pressing health problems.

Appendix A

Workshop Agenda

Innovation in Drug Research and Development for Prevalent Chronic Diseases—A Three-Part Virtual Workshop

February 22, March 1, and March 8, 2021

Half of all Americans live with at least one chronic disease, such as heart disease, cancer, stroke, or diabetes. These and other chronic diseases are the leading cause of death and disability in the United States and are a leading driver of health care costs. Yet, investment in the leading causes of death and disability, other than cancer, has not kept pace with the public health need. This virtual public workshop will provide a venue for stakeholders to examine bottlenecks to innovation in drug research and development (R&D) for prevalent chronic diseases and highlight opportunities for spurring drug R&D in this space.

The virtual workshop will be conducted in three parts:

- Part One (February 22, 2021) will discuss key opportunities and challenges for increasing investment, broadening biospecimen collection and registry use, and supporting innovative discovery and preclinical research in prevalent chronic diseases.

- Part Two (March 1, 2021) will consider key aspects and opportunities related to development, translation, regulation, and support for innovative clinical research in prevalent chronic diseases.
- Part Three (March 8, 2021) will consider case studies in both discovery and clinical research related to prevalent chronic diseases, and discuss potential cross-cutting applications for other prevalent chronic diseases.

For additional information on this virtual workshop, please visit the main project page.

Part One: February 22, 2021
Opportunities in Discovery and Preclinical Research for Prevalent Chronic Diseases
11:00 am–3:00 pm ET

11:00 am **Welcome and Opening Remarks**

Carlos Garner, *Workshop Co-Chair*
Vice President, Global Regulatory Affairs
Eli Lilly and Company

Anantha Shekhar, *Workshop Co-Chair*
Senior Vice Chancellor for Health Sciences and Dean of the School of Medicine
University of Pittsburgh

SESSION I OVERVIEW OF R&D FOR PREVALENT CHRONIC DISEASES

Session Objectives:

- Discuss the unique cross-cutting challenges facing preclinical research for prevalent chronic diseases; and
- Highlight opportunities to overcome those challenges and mobilize the R&D innovation engine.

11:10 am **A Patient's Perspective on Mobilizing the R&D Innovation Engine**
Russ Paulsen
Chief Operating Officer
UsAgainstAlzheimer's

SESSION II FUNDING AND INVESTMENT DECISION MAKING IN DISCOVERY RESEARCH

Session Objectives:

- Examine common causes of failures in discovery research for prevalent chronic diseases and how failures could be avoided or "go/no-go" decisions could be accelerated in the future;
- Discuss whether investment and cultural incentives are in alignment for spurring the type of R&D that will address unmet need when it comes to prevalent chronic diseases; and
- Consider the factors that determine which research areas key decision makers (e.g., investors, sponsors, researchers) decide to move forward.

11:25 am **Response and Overview**
SUSAN SCHAEFFER, *Moderator*
President and Chief Executive Officer
Patients' Academy for Research Advocacy

11:35 am **Funder Perspective**
JASON MELLAD
Chief Executive Officer and Founder
Start Codon

11:50 am **Public–Private Partnership Investor Perspective**
JOSEPH MENETSKI
Associate Vice President of Research Partnerships
Foundation for the National Institutes of Health

12:05 pm **Moderated Panel Discussion and Audience Q&A**

12:30 pm **BREAK** (*30 minutes*)

SESSION III BIOSPECIMEN COLLECTION AND REGISTRY USE IN DISCOVERY RESEARCH

Session Objectives:

- Consider lessons learned from other disease areas that could have cross-cutting applications for prevalent chronic diseases; and
- Discuss the availability or need for high-quality biospecimen repositories and datasets that represent the patient populations most impacted by prevalent chronic diseases.

1:05 pm **Introduction and Overview**
HOWARD B. ROSEN, *Moderator*
Managing Director, BonVelo Ventures
Lecturer, Stanford University

1:10 pm **Academic Perspective**
ERICA WOODAHL
Professor, Department of Biomedical and Pharmaceutical Sciences
University of Montana

SESSION IV NEW TECHNOLOGIES ENABLING DISCOVERY RESEARCH

Session Objectives:

- Discuss the unique cross-cutting challenges in preclinical research for prevalent chronic diseases and consider how new technologies could help researchers overcome these challenges; and
- Consider lessons learned from other disease areas for which new technologies have been a key driver of progress.

1:25 pm **Academic Discovery Science–Technology Perspective**
JOHN NGAI
Director
BRAIN Initiative, National Institutes of Health

1:40 pm **Artificial Intelligence for Discovery Science**
ANDREW A. RADIN
Chief Executive Officer
twoXAR Pharmaceuticals

1:55 pm **Regulator Perspective**
QI LIU
Senior Science Advisor, Office of Clinical Pharmacology & Translational Sciences
U.S. Food and Drug Administration

2:10 pm **Moderated Panel Discussion and Audience Q&A**

2:50 pm **Closing Remarks**
CARLOS GARNER, *Workshop Co-Chair*
Vice President, Global Regulatory Affairs
Eli Lilly and Company

ANANTHA SHEKHAR, *Workshop Co-Chair*
Senior Vice Chancellor for Health Sciences and Dean of the School of Medicine
University of Pittsburgh

3:00 pm **ADJOURN**

Part Two: March 1, 2021
Opportunities in Clinical Research for Prevalent Chronic Diseases
11:00 am–3:00 pm ET

11:00 am **Welcome and Opening Remarks**
CARLOS GARNER, *Workshop Co-Chair*
Vice President, Global Regulatory Affairs
Eli Lilly and Company

ANANTHA SHEKHAR, *Workshop Co-Chair*
Senior Vice Chancellor for Health Sciences and Dean of the School of Medicine
University of Pittsburgh

SESSION I OVERVIEW OF R&D FOR PREVALENT CHRONIC DISEASES

Session Objectives:

- Discuss the unique cross-cutting challenges facing clinical research for prevalent chronic diseases; and
- Highlight opportunities to overcome those challenges and mobilize the R&D innovation engine.

11:10 am **A Patient's Journey**
CHRISTIN VEASLEY
Co-Founder and Director
Chronic Pain Research Alliance

11:25 am **Mobilizing the R&D Innovation Engine**
CHRONIS MANOLIS
Senior Vice President of Pharmacy
University of Pittsburgh Medical Center Health Plan

SESSION II INVESTMENT AND FUNDING DECISIONS IN CLINICAL RESEARCH

Session Objectives:

- Discuss whether investment and cultural incentives are in alignment for spurring the type of R&D that will address unmet need when it comes to prevalent chronic diseases; and
- Consider the factors that determine which clinical programs key decision makers (e.g., investors, sponsors, and researchers) decide to move forward.

11:35 am **Economics Perspective**
KIRSTEN AXELSEN
Visiting Fellow
American Enterprise Institute

11:50 am **A Payer's Perspective: Pricing and Health Economic Drivers That Incentivize Development Investments**
KEN EHLERT
Chief Scientific Officer
UnitedHealth Group

12:05 pm **Moderated Panel Discussion and Audience Q&A**

12:25 pm **BREAK** (*30 minutes*)

SESSION III INNOVATIVE APPROACHES TO EFFICIENT CLINICAL DEVELOPMENT

Session Objectives:

- Discuss the unique cross-cutting challenges in clinical trials for prevalent chronic diseases (e.g., are the regulatory requirements predictable?);
- Brainstorm and prioritize potential strategies to decrease costs and risks for development (i.e., highlight innovative ways to design clinical trials); and
- Discuss ways to meaningfully engage communities and patients in clinical trials.

1:00 pm **Introduction and Overview**
BETTINA DRAKE, *Moderator*
Professor, Washington School of Medicine
Associate Director of Community Outreach and Engagement
Alvin J. Siteman Cancer Center

1:05 pm **Community Health Researcher Perspective**
KAREN WINKFIELD
Executive Director
Meharry-Vanderbilt Alliance

1:15 pm **Industry (Regulatory Lead) Perspective**
MICHELLE ROHRER
Senior Vice President, Global Head of Product Development Regulatory & Policy
Roche

1:30 pm **Regulatory Perspective**
JAMES P. SMITH
Deputy Director, Division of Clinical Policy, Office of New Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

SESSION IV NEW TECHNOLOGIES ENABLING INNOVATIVE CLINICAL RESEARCH

Session Objectives:

- Discuss the unique cross-cutting challenges in clinical research for prevalent chronic diseases and consider how new technologies could help researchers overcome these challenges; and
- Consider lessons learned from other disease areas where new technologies have been a key driver of progress.

1:50 pm **Biotech Perspective**
GRACE COLÓN
Chief Executive Officer
InCarda Therapeutics

2:05 pm **Regulatory Perspective**
ELIZABETH KUNKOSKI
Clinical Methodology Team, Office of Medical Policy
U.S. Food and Drug Administration

2:20 pm **Moderated Panel Discussion and Audience Q&A**

2:50 pm **Closing Remarks**
CARLOS GARNER, *Workshop Co-Chair*
Vice President, Global Regulatory Affairs
Eli Lilly and Company

ANANTHA SHEKHAR, *Workshop Co-Chair*
Senior Vice Chancellor for Health Sciences and Dean of the School of Medicine
University of Pittsburgh

3:00 pm **ADJOURN**

Part Three: March 8, 2021
Case Studies in Prevalent Chronic Disease Research
11:00 am–3:00 pm ET

11:00 am **Welcome and Opening Remarks**
CARLOS GARNER, *Workshop Co-Chair*
Vice President, Global Regulatory Affairs
Eli Lilly and Company

ANANTHA SHEKHAR, *Workshop Co-Chair*
Senior Vice Chancellor for Health Sciences and Dean of the School of Medicine
University of Pittsburgh

SESSION I CASE STUDIES ACROSS THE R&D LIFE CYCLE: MOBILIZING COMMUNITIES AND RESOURCES, ANALYZING PAST SUCCESS

Session Objectives:

- Consider lessons learned in research across the R&D life cycle in several disease areas that could have cross-cutting applications for many prevalent chronic diseases.
  - Discuss how research and patient communities have been mobilized to address discovering treatments for some example diseases, and how those approaches led to success.
  - Discuss examples of successful development for prevalent chronic disease treatments and what aspects of those approaches led to success.
- Discuss potential strategies to spur drug R&D innovation for prevalent chronic diseases.

11:10 am **Introduction and Overview**
GRACE COLÓN, *Moderator*
Chief Executive Officer
InCarda Therapeutics

11:20 am **Success Story from Cystic Fibrosis**
ROBERT K. COUGHLIN
Managing Director, Life Sciences, JLL
Former President and Chief Executive Officer, MassBio

11:35 am **Digital Innovation for Treating Prevalent Chronic Diseases**
RAOLAT ABDULAI
Global Clinical Lead, Immunology & Inflammation
Sanofi

11:50 am **Investing in One Treatment, Applying to Multiple Diseases**
ROBERT HEINE
Distinguished Eli Lilly Scholar
Eli Lilly and Company

12:05 pm **Moderated Panel Discussion and Audience Q&A**
Discussion Questions:

- *How can patient advocacy affect drug research and development?*
- *What can we learn from these examples about psychiatric disorders, cardiology, or other prevalent chronic diseases?*
- *How might success be replicated, and what might the investment look like for other prevalent chronic disease areas?*
- *What options exist for trials examining multiple indications?*
- *How might these successes be replicated or apply in the future, and what might the investment look like for other prevalent chronic disease areas?*
- *How have digital advancements changed approaches to developing treatments for prevalent chronic diseases, and how might they affect development in the future?*

12:45 pm **BREAK** (*30 minutes*)

SESSION II RECAP AND POTENTIAL FUTURE STRATEGIES

Session Objectives:

- Reflect on approaches and potential strategies to spur drug R&D innovation for prevalent chronic diseases; and
- Brainstorm potential strategies to spur drug R&D innovation for prevalent chronic diseases (i.e., highlight promising avenues forward that merit additional time, effort, funding, or attention).

1:15 pm **Summary Presentations by Session Moderators** (*10 minutes each*)
Grace Colón
Chief Executive Officer
InCarda Therapeutics

Bettina Drake
Professor, Washington School of Medicine
Associate Director of Community Outreach and Engagement
Alvin J. Siteman Cancer Center

Howard B. Rosen
Managing Director, BonVelo Ventures
Lecturer, Stanford University

Susan Schaeffer
President and Chief Executive Officer
Patients' Academy for Research Advocacy

1:55 pm **Moderated Panel Discussion and Audience Q&A**
Discussion Questions:

- *Are there common characteristics of disease areas routinely more affected than others by either discovery and preclinical- or clinical-stage research barriers?*
- *What cross-cutting strategies could enable investment?*
- *How might overall risk for stakeholders innovating in prevalent chronic disease treatments be lowered, with an eye toward integrating policy with stimulus?*

2:50 pm **Closing Remarks**
Carlos Garner, *Workshop Co-Chair*
Vice President, Global Regulatory Affairs
Eli Lilly and Company

Anantha Shekhar, *Workshop Co-Chair*
Senior Vice Chancellor for Health Sciences and Dean of the School of Medicine
University of Pittsburgh

3:00 pm **ADJOURN**

Appendix B

Biographical Sketches of Workshop Speakers

Raolat Abdulai, M.D., M.M.Sc., serves as a global clinical lead for the Immunology and Inflammation division at Sanofi. In this position, she acts as the clinical strategic lead on projects with a focus of bringing transformational medicines to those with immune-driven diseases. In addition to her drug development role, she collaborates to advance technology that transforms the product life cycle for faster and more efficient clinical trials: integrating innovative tools and methods to disrupt traditional clinical research paradigms, using real-world data to understand the patient journey for better decision making, and incorporating wearables and digital tools into clinical trials. She has been a featured panelist at several conferences, including MassBio Digital Health Impact, BIO Digital 2020, and FierceAI week. In 2020, she was named by the Commonwealth Institute as one of the Extraordinary Women Advancing Healthcare.

Dr. Abdulai has an M.M.Sc. in biomedical informatics from Harvard Medical School. She attended medical school at the Howard University College of Medicine, completed internal medicine training at the Mayo Clinic in Rochester, Minnesota, and the Pulmonary and Critical Care fellowship at Brigham and Women's Hospital in Boston, Massachusetts. She is triple board certified and continues to practice by volunteering at a Boston-based community health center, where she treats patients with respiratory diseases. While in medical school, Dr. Abdulai co-founded the New Freedmen's clinic to provide free holistic care to the uninsured and underinsured local population. In 2009, Dr. Abdulai was featured in *O! Oprah* Magazine as one of 80 inspirational women entrepreneurs from around the country for the *O! Oprah* Magazine–White House Project Leadership Conference.

Among her many other honors, Dr. Abdulai was invited to the White House for President Obama's Innovative Programs Summit, which highlighted impactful social entrepreneurship programs across the country. Her passions include ensuring digital health equity and increasing access to clinical trials for women and people of color. Her personal project into this area was chosen for the Harvard iLab Venture Incubation Program.

Kirsten Axelsen, M.S., works with leaders in health care and builds diverse and effective teams, helping to develop business practices that lead to affordable medicines, positive public perception, and sustained investment in scientific advancement. Ms. Axelsen was on the leadership team of Pfizer Inc.'s $30 billion global innovative pharmaceutical business, where she led strategy and business evaluation. Previously, Ms. Axelsen led Pfizer's global policy team. She is currently a visiting scholar with the American Enterprise Institute, an Aspen Institute Health Innovator Fellow, and a consultant acting as a senior policy advisor to DLA Piper and Charles River Associates. She is a founder and the executive secretary of the Preparedness and Treatment Equity Coalition, an organization focused on identifying metrics and reimbursement pathways to achieve greater equity in health care.

Grace E. Colón, Ph.D., brings more than 25 years of experience in biopharma, genomics, health care, and industrial biotechnology. She is currently the chief executive officer (CEO), president, and director at InCarda Therapeutics, a clinical stage therapeutics company developing a new treatment for atrial fibrillation. She is also the executive chairman (formerly CEO) of ProterixBio, and serves on the boards of CareDx, the MIT Corporation (MIT Board of Trustees), and the Biotechnology Innovation Organization. Formerly, she was a partner at New Science Ventures, a New York–based venture capital firm with more than $700 million under management, and served on the boards of Paradigm Diagnostics, PerceptiMed, Cocoon Biotech, and on the Advisory Board of the Miller Center for Social Entrepreneurship at Santa Clara University.

Previously, she co-founded Pyranose Biotherapeutics, a biologics discovery platform company. She was also the founding president of the Industrial Products Division at Intrexon Corporation, where she established a new division focused on leveraging synthetic biology for bioindustrial applications such as biofuels and renewable chemicals. Prior to Intrexon, she was the head of clinical operations for Gilead Sciences, where she was responsible for the global execution of clinical trials. She also created and led both the Alliance Management and Commercial Strategic Planning groups. Prior to Gilead, she was the vice president of corporate planning at Affymetrix, where she was responsible for strategic planning and project management and where she also served as the chief of operations for the

International Genomics Consortium, a nonprofit medical research organization focused on cancer genomics. Earlier in her career she was a consultant with McKinsey & Co., where she served clients in health care, biotech, high tech, and venture capital. She was also an engineer with Merck & Co. in France and in Rahway, New Jersey.

Dr. Colón received her Ph.D. in chemical engineering from the Massachusetts Institute of Technology, where she was a National Science Foundation fellow. She also holds a B.S. in chemical engineering from the University of Pennsylvania, where she was a Benjamin Franklin Scholar.

Robert K. Coughlin is the managing director of life sciences at JLL. Most recently, Mr. Coughlin served as the president and the chief executive officer at MassBio. In this role, his mission was to advance Massachusetts' leadership in the life sciences to grow the industry, add value to the health care system, and improve patient lives. Over 14 years, he truly became a champion for patients by ensuring innovative companies have the best environment possible to research, develop, and commercialize breakthrough therapies and cures for people around the world who need and deserve them. He played an integral role in making Massachusetts the best place in the world for the life science industry.

Mr. Coughlin has spent his career in both the public and private sectors. Before joining MassBio, he served as the undersecretary of economic development within Governor Deval Patrick's administration, where he prioritized both health care and economic development issues and was a strong advocate for the life sciences industry in Massachusetts. Prior to that, he was elected as State Representative to the 11th Norfolk district for three terms. He has also held senior executive positions in the environmental services, capital management, and venture capital industries.

In addition to his professional responsibilities, Mr. Coughlin is an active member in the community. He is a past board member of the Massachusetts Maritime Academy and the Beth Israel Deaconess Hospital and is currently serving on the board of directors for The Schwartz Center for Compassionate Healthcare, Franciscan Children's Hospital, and MassBio. He also serves on the board of directors of Synspira Therapeutics and Boston Analytical. Mr. Coughlin has served as the honorary chair of the Great Strides Cystic Fibrosis Walk since 1996. In years past, he co-chaired the Children's Hospital Boston signature event, Champions for Children's, and The Schwartz Center for Compassionate Healthcare dinner. He is a graduate of the Massachusetts Maritime Academy, where he majored in marine engineering, and served as an officer in the U.S. Naval Reserve.

Bettina F. Drake, Ph.D., M.P.H., is a professor of surgery at the Washington University School of Medicine and the Siteman Cancer Center. As an epi-

demiologist, her research has focused on identifying preventive strategies to reduce health disparities in cancer and other chronic disease outcomes. In addition, she co-leads the Prostate Cancer Community Partnership, a community partnership of PECaD, which seeks to reduce prostate cancer disparities in the region. She is most interested in how her community-based work informs and strengthens her epidemiology findings. Information gained from community-based studies informs both study design and recruitment strategies. In turn, the results of the cancer prevention work can be disseminated in collaboration with community partners. Dr. Drake also teaches intermediate clinical epidemiology in the Master of Population Health Sciences program. Dr. Drake earned her Ph.D. in epidemiology at the University of South Carolina Arnold School of Public Health and completed postdoctoral studies at the T.H. Chan Harvard School of Public Health.

Ken Ehlert is the chief scientific officer, leading UnitedHealth Group's research and development (R&D) function, an innovation engine intended to positively impact patient health on a global scale. UnitedHealth Group's R&D efforts are driven by math, data, and clinical science, but also focus on the human connections required to understand, manage, and prevent the chronic diseases that afflict nearly half of the world's population. Mr. Ehlert has worked with UnitedHealth Group since 2004 and became the chief scientific officer in 2017. Previously the co-founder and the chief executive officer of Savvysherpa, Mr. Ehlert has spent his career building products and businesses that improve the health care system.

Robert J. Heine, M.D., Ph.D., FRCP, joined Lilly Diabetes in January 2008. He was the vice president of global medical affairs for Lilly Diabetes until 2014. In his current position, he is responsible for the medical and scientific strategy, development of external research partnerships, and global medical education. Before joining Lilly he was a professor of diabetology in the Department of Endocrinology and the director of the Diabetes Centre at the VU University Medical Center in Amsterdam. His main research areas included epidemiology and type 2 diabetes pathophysiology. Dr. Heine has held several key positions within the European Association for the Study of Diabetes (EASD), including the honorary treasurer and a member of the Executive Committee, and was the president of the Organizing Committee for the 2007 Meeting of the EASD, Amsterdam. Dr. Heine has served as associate editor of *Diabetic Medicine*, and has been a member of the editorial boards of several diabetes journals. To date, he has authored or co-authored more than 450 peer-reviewed papers and reviews.

Elizabeth Kunkoski, M.S., currently works in the U.S. Food and Drug Administration's Center for Drug Evaluation and Research's Office of Med-

ical Policy. She oversees several projects involving digital health technologies and electronic health records and storage in clinical investigations. She worked for 15 years in the Center for Devices and Radiological Health in guidance document development and as a branch chief overseeing the review of orthopedic devices. She earned an M.S. in biomedical engineering and a bachelor's degree in chemical engineering from the University of Michigan.

Qi Liu, Ph.D., M.S., is a senior science advisor in the Office of Clinical Pharmacology (OCP) at the U.S. Food and Drug Administration (FDA). At FDA, Dr. Liu contributed to the review of more than 200 New Drug Applications/Supplemental New Drug Applications, 20 Biologics License Applications/Supplemental Biologics License Applications, and numerous Investigational New Drug Applications. Dr. Liu co-authored about 40 manuscripts and presented on many topics at Advisory Committee meetings and scientific conferences. She worked on several working groups for FDA guidances and the Manual of Policies & Procedures development. Dr. Liu is the lead of OCP's Innovative Data Analytics program and was the vice chair of the OCP Biologics Oversight Board. Dr. Liu is on the editorial board of *Clinical and Translational Science*, *Clinical Pharmacology & Therapeutics*, and the *AAPS Journal*. Before joining FDA, Dr. Liu was a senior pharmacokineticist at Merck. She obtained a Ph.D. in pharmaceutics and an M.S. in statistics from the University of Florida.

Chronis Manolis, R.Ph., oversees the pharmacy programs for the Health Plan's Medicare, Medical Assistance, and commercial products. Mr. Manolis has more than 30 years of experience in the pharmacy and managed care industry. He previously held management positions with Medco Health Solutions and Stadtlanders Specialty Pharmacy Services. Mr. Manolis is also an adjunct instructor at the University of Pittsburgh School of Pharmacy. He holds a bachelor's degree in pharmacy from the University of Pittsburgh.

Jason Mellad, Ph.D., is a scientist entrepreneur passionate about translating innovative technologies into more effective therapies and better patient outcomes. He founded Start Codon to identify and recruit high-potential and disruptive health care startups worldwide, seed fund them, and leverage the exceptional resources of the Cambridge (United Kingdom) Cluster with an aim to minimize risk and drive their success. Previously, Dr. Mellad was the chief executive officer of Cambridge Epigenetix, which has developed a proprietary epigenetic biomarker discovery platform for the development of new diagnostic assays and the identification of novel drug targets. While at Cambridge Epigenetix, he transformed the research tools company into a leading liquid biopsy player and led two successful fundraisers

(Series B and C) for a total of $49.8 million. Dr. Mellad was awarded a Marshall Scholarship to obtain his Ph.D. in medicine from the University of Cambridge with a focus on the molecular mechanisms regulating vascular remodeling within coronary artery bypass grafts.

Joseph P. Menetski, Ph.D., is an associate vice president of research partnerships and the director of the Biomarkers Consortium at the Foundation for the National Institutes of Health. Dr. Menetski received his Ph.D. from the Northwestern University Feinberg School of Medicine with Dr. Stephen Kowalczykowski and completed his postdoctoral training at the Laboratory of Molecular Biology at the National Institute of Diabetes and Digestive and Kidney Diseases at the National Institutes of Health with Dr. Martin Gellert. He then started his career in industry in 1993 in the Immunopathology Department at Parke-Davis (later Pfizer), where he established a discovery research program in cellular inflammation that eventually transitioned to the molecular study of osteoarthritis. Dr. Menetski moved to Merck in 2004. His first position was in the Department of Immunology, where he was involved in the osteoarthritis new targets and biomarker program. While at Merck he was a member of the Molecular Profiling group, the Knowledge Discovery and Knowledge Management group, and finally a director in global competitive intelligence. Over the years, he has been a key contributor to many basic research and clinical programs in the areas of arthritis, sarcopenia, osteoporosis, and asthma. He has served as a core research team member on several external basic research projects for identification of new targets and molecular biomarkers. His industry research and development (R&D) experiences include target identification, compound selection, translational biomarker identification, clinical study design and analysis, and external scientific collaborations. In the commercial space, he has been intimately involved in opportunity and asset identification and qualification, and in assessing the competitive landscape of disease areas that he is supporting. During this time, he has been recognized by multiple R&D awards for his contributions.

John J. Ngai, Ph.D., is the director of the National Institutes of Health's (NIH's) Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative. Dr. Ngai earned his bachelor's degree in chemistry and biology from Pomona College, Claremont, California, and Ph.D. in biology from the California Institute of Technology (Caltech) in Pasadena. He was a postdoctoral researcher at Caltech and at the Columbia University College of Physicians and Surgeons before starting his faculty position at the University of California, Berkeley. During more than 25 years as a Berkeley faculty member, Dr. Ngai has trained 20 undergraduate students, 24 graduate students, and 15 postdoctoral Fellows in addition to teaching more

than 1,000 students in the classroom. His work has led to the publication of more than 70 scientific articles in some of the field's most prestigious journals and 10 U.S. and international patents. Dr. Ngai has received many awards including from the Sloan Foundation, The Pew Charitable Trusts, and the McKnight Endowment Fund for Neuroscience. As a faculty member, Dr. Ngai has served as the director of Berkeley's Neuroscience Graduate Program and the Helen Wills Neuroscience Institute. He has also provided extensive service on NIH study sections, councils, and steering groups, including as previous co-chair of the NIH BRAIN Initiative Cell Census Consortium Steering Group. Dr. Ngai will oversee the long-term strategy and day-to-day operations of the NIH BRAIN Initiative as it takes on the challenges of the next 5-year plan.

Russ Paulsen, M.A., is the chief operating officer (COO) of UsAgainstAlzheimer's and UsAgainstAlzheimer's Action, which bring all of us together to win the fight against Alzheimer's disease and related dementias. As COO, Mr. Paulsen leads the program, fundraising, finance, and government relations and policy teams. Before joining UsAgainstAlzheimer's, Mr. Paulsen held executive positions at the United Way and the American Red Cross, working on nationwide challenges in social service and public health. His team helped tens of thousands across the Gulf Coast and created the model for Red Cross long-term recovery programs when he headed up recovery after Hurricane Katrina. Then, the public health campaign his team created around reduction of deaths and injuries from home fires has saved more than 800 lives and made more than 870,000 American homes safer since 2014.

Andrew Radin, M.S., combining his experience as an entrepreneur and a technologist with his passion for social responsibility, co-founded Aria Pharmaceuticals to develop life-saving medicines to help treat patients in need. Prior to co-founding Aria, Mr. Radin held chief technology officer roles at several early-stage companies where he managed teams as large as a hundred technologists throughout the world. Mr. Radin developed the company's proprietary platform and as the chief executive officer is focused on overall company strategy, product development, and fundraising. Mr. Radin studied biomedical informatics in Stanford University's SCPD graduate program and holds an M.S. and a B.S. in computer science from the Rochester Institute of Technology.

Michelle Rohrer, Ph.D., is the global head of product development regulatory at Roche. Dr. Rohrer joined Genentech, a member of the Roche group, 28 years ago as a postdoctoral research fellow and later became a clinical scientist before moving to regulatory in 1999. Dr. Rohrer has held

a number of leadership positions over the years within product development and regulatory, including the head of U.S. regulatory and site head for product development at the South San Francisco site. Prior to becoming the global head of product development regulatory, she held the position of global head of regulatory regions and policy. In her current position, Dr. Rohrer leads the global regulatory organization overseeing Roche's regulatory development strategies and policy efforts worldwide.

In 2013, Dr. Rohrer was named by the *SF Business Times* as one of "The Most Influential Women in Bay Area Business." In 2014, she was selected by PharmaVOICE as one of the 100 most inspiring leaders in health care. Dr. Rohrer served on the Genentech Foundation Board for 3 years helping to oversee Genentech's charitable giving. Since 2014, she has served on the Science Advisory Board for the University of California, San Francisco–Stanford Center for Excellence in Regulatory Science. In 2015 she was selected and served as one of the industry representatives to the U.S. Food and Drug Administration–industry team, which negotiated the Prescription Drug User Fee Act VI draft agreement, which is now under legislative review. In 2016 she joined the Board of TransCelerate Biopharma and currently serves as the board chair. Dr. Rohrer received her Ph.D. in nutrition science with a minor in physiological biochemistry from the University of California, Davis.

Howard B. Rosen, M.B.A., is an independent consultant and serves on the board of directors of AcelRx Pharmaceuticals, Inc.; Alcobra, Ltd.; where he has served as the chair since 2014, ALDEA Pharmaceuticals, Inc.; Entrega, Inc.; Kala Pharmaceuticals, Inc., where he has served as the chair since 2014; and PaxVax, Inc., where he has served as the chair since 2011. From 2004 to 2008, he was the vice president of commercial strategy at Gilead Sciences, Inc., where his responsibilities included strategic marketing, global brand management, health economics, competitive intelligence, market research, and Gilead's overall portfolio and business planning.

Prior to joining Gilead, Mr. Rosen was the president of the ALZA Corporation where he was responsible for all aspects of managing ALZA as an independent 1,000-person operating company within the Johnson & Johnson Family of Companies. Previously at ALZA as the vice president of product development, he was responsible for product development activities, portfolio management, and corporate and new product planning. Over his 10 years at ALZA, Mr. Rosen also had responsibilities for mergers and acquisitions, research and development planning, and technology ventures. Prior to joining ALZA, Mr. Rosen managed the west coast practice of Integral, Inc., was the director of corporate development at GenPharm International, Inc., and was a consultant in the San Francisco office of McKinsey & Co. Mr. Rosen was a member of the Stanford University Advi-

sory Council on Interdisciplinary Biosciences from 2003 to 2011 and the Stanford School of Engineering Advisory Council from 2004 to 2007. Mr. Rosen is a member of the Biomedical Engineering Advisory Board at the City College of New York and the board of directors of the Massachusetts of Institute of Technology (MIT) Club of Northern California. Previously he was a member of the board of directors of CNS Therapeutics, Inc.; CoTherix, Inc.; NTF Therapeutics, Inc.; and Pearl Therapeutics, Inc., where he served as the interim president and the chief executive officer from June 2010 to March 2011, and Pharsight Corporation.

Mr. Rosen is a lecturer in the Department of Chemical Engineering at Stanford University and a lecturer in management at the Stanford Graduate School of Business. He is also a member of the National Academy of Engineering (NAE), where he is the chair of the Bioengineering Section, and a fellow of the American Institute for Medical and Biological Engineering. He is the co-inventor on seven U.S. patents. Mr. Rosen received an M.B.A. from the Stanford Graduate School of Business, where he graduated first in his class as the Henry Ford II Scholar. Mr. Rosen has an M.S. in chemical engineering from MIT and he graduated with distinction from Stanford University with a B.S. in chemical engineering.

Susan Schaeffer founded the Patients' Academy for Research Advocacy in 2018 after spending 15 years informing and educating biopharma industry stakeholders on best practices and new thinking in clinical development, regulation, pricing, and market access. In 2002, Ms. Schaeffer dedicated her career to learning about and improving drug development after the loss of a close friend to breast cancer at a very early age. She joined the biopharmaceutical industry journal *BioCentury* as a staff writer in 2003, with no background in science or the biopharmaceutical industry, learning about the business and science of developing drugs by interviewing chief executive officers and scientists about their work. Ms. Schaeffer became the managing editor of *BioCentury* and the daily news digest *BioCentury Extra* in 2004, led *BioCentury*'s product discovery and development coverage as the senior editor from 2010 through 2012, and took the helm of the publication in 2012. As the chief editor, Ms. Schaeffer became an early champion of patient-centered research and development (R&D) as an essential practice for translating great science into medicines that patients really want and society will pay for. Her work has been cited in regulatory filings and has influenced global biopharmaceutical companies to begin working on pricing experiments that can improve access to health care innovation.

In January 2020, Ms. Schaeffer was appointed as member of the Forum on Drug Discovery, Development, and Translation, a group of leaders organized by the the National Academies of Sciences, Engineering, and Medicine to address issues related to drug R&D. She is a frequent speaker

at private and public meetings, including the annual BIO International Convention, The Leaders in Global Health and Technology (LIGHT) Forum, the rEVOLUTION Symposium for CSOs, and the Milken Institute's Future of Health Summit. She holds a B.F.A. in painting from the San Francisco Art Institute.

James P. Smith, M.D., M.S., is the deputy director of the Division of Clinical Policy in the Office of New Drug Policy in the Office of New Drugs (OND) at the U.S. Food and Drug Administration (FDA). In this capacity, he primarily works on clinical and scientific policy priorities of OND. He was previously responsible for overseeing development programs targeting lipid disorders and obesity as the deputy division director of the Division of Metabolism and Endocrinology Products. Prior to joining FDA in February 2011, he was a faculty member in the Division of Nephrology of the University of Michigan Health System. Dr. Smith is a graduate of the University of Michigan Medical School, and he completed his residency in internal medicine at the same institution. Subsequently, he completed fellowships in both nephrology and clinical pharmacology at the Vanderbilt University Medical Center and a master's degree in clinical research design and statistical analysis at the University of Michigan School of Public Health.

Christin Veasley is the co-founder and the director of the Chronic Pain Research Alliance. She has lived with chronic pain since surviving a near-fatal accident in her teens. Her health experiences led her to pursue a B.S., spend time conducting neuroscience research at the Johns Hopkins University School of Medicine, and join the research advocacy community. Her life's work has been to advocate for the acceleration of rigorous multidisciplinary pain research and the translation of research findings into meaningful change for people with chronic pain—with a special emphasis on pain conditions that are common in women and frequently co-occur. She has been a passionate advocate at the congressional and federal agency levels for bringing about public awareness of the profound impact of chronic pain, the urgent need for an increased federal research investment to address this public health crisis, and the long-overlooked value of including patient perspectives in all aspects of the research continuum. For more than 20 years, she has served in several nonprofit management and leadership positions. She holds advisory positions for numerous critical pain initiatives within federal agencies, such as the National Institutes of Health, the Centers for Disease Control and Prevention, and the U.S. Food and Drug Administration. She is also involved in academic pain research studies and various collaborative alliances and public–private partnerships working to promote pain research, treatment, and education. Ms. Veasley has authored journal articles, op-eds, book chapters, continuing medical

education programs for health care providers, patient tutorials, and self-help guides. To promote awareness, she speaks openly about her experience with chronic pain and its profound impact on her life. Ms. Veasley has been a presenter at more than 30 medical, research, and policy conferences, as well as federal agency meetings, and has been interviewed for print, television, and radio media.

Karen Winkfield, M.D., Ph.D., is the executive director of the Meharry-Vanderbilt Alliance, a strategic partnership between the Meharry Medical College and the Vanderbilt University Medical Center. Her primary responsibilities include working closely with the Vanderbilt University Medical Center and the Meharry Medical College to ensure their investigators have access to expert faculty collaborators, core resources, and services to catalyze innovative research. She is a national expert in community engagement, with research focused on the design and implementation of programming to reduce sociocultural and economic barriers that contribute to disparate health outcomes for racial/ethnic minorities and underserved populations.

Previously, Dr. Winkfield was an associate professor of radiation oncology at Wake Forest University, the associate director for community outreach and engagement, and the director of the Office of Cancer Health Equity at the Wake Forest Baptist Comprehensive Cancer Center. Prior to joining Wake Forest in August 2016, Dr. Winkfield was a radiation oncologist at the Massachusetts General Hospital Cancer Center. She specializes in the use of radiation therapy in the treatment of hematologic malignancies (lymphoma, leukemia, multiple myeloma, bone marrow transplantation) and breast cancer. She developed the first comprehensive clinical program focused on hematologic malignancies in the Department of Radiation Oncology at Massachusetts General Hospital. With support of collaborating oncologists, she also established the first multidisciplinary clinic for patients with hematologic disorders. While at Massachusetts General Hospital, Dr. Winkfield was a co-principal investigator of a $3 million grant that established the Lazarex–MGH Cancer Care Equity Program, a program designed to improve clinical trial access and enrollment in vulnerable populations. She was responsible for the community outreach and education component of the grant, and continued that work at Wake Forest.

Erica Woodahl, Ph.D., is a professor in the Department of Biomedical and Pharmaceutical Sciences in the Skaggs School of Pharmacy at the University of Montana. Dr. Woodahl received a B.S. in biochemistry at the University of Notre Dame in 1998 and a Ph.D. from the Department of Pharmaceutics at the University of Washington in 2004. She completed a postdoctoral fellowship in clinical pharmacokinetics at the Fred Hutchinson Cancer Research Center in Seattle. She joined the faculty at the University of Montana in

2007 as an assistant professor and was promoted to associate professor in 2012 and a professor in 2020. Dr. Woodahl teaches pharmacokinetics and pharmacogenomics and uses community-based participatory research to address complex and important challenges in conducting precision medicine research with underserved populations.