Applying an Implementation Science Approach to Genomic Medicine: Workshop Summary

DETAILS

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APPLYING AN IMPLEMENTATION SCIENCE APPROACH TO GENOMIC MEDICINE

WORKSHOP SUMMARY

Siobhan Addie, Steve Olson, and Sarah H. Beachy, *Rapporteurs*

Roundtable on Translating Genomic-Based Research for Health

Board on Health Sciences Policy

Health and Medicine Division

The National Academies of
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This workshop summary has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published workshop summary as sound as possible and to ensure that the workshop summary meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the process. We wish to thank the following individuals for their review of this workshop summary:

VENCE L. BONHAM, JR., National Human Genome Research Institute
LAURENCE MEYER, Salt Lake City Veterans Administration Medical Center
JANE PERLMUTTER, Gemini Group
ENOLA PROCTOR, Washington University in St. Louis

Although the reviewers listed above have provided many constructive comments and suggestions, they did not see the final draft of the workshop summary before its release. The review of this workshop summary was overseen by **MELVIN WORTH.** He was responsible for making certain that an independent examination of this workshop summary was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this workshop summary rests entirely with the rapporteurs and the institution.

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Abbreviations and Acronyms

ACMG	American College of Medical Genetics and Genomics
ASCO	American Society of Clinical Oncology
CDC	Centers for Disease Control and Prevention
cffDNA	cell-free fetal DNA
CFIR	Consolidated Framework for Implementation Research
CPTP	Canadian Partnership for Tomorrow Project
EBP	evidence-based practice
EGAPP	Evaluation of Genomic Applications in Practice and Prevention
EHR	electronic health record
FDA	U.S. Food and Drug Administration
GWAS	genome-wide association study
IGNITE	Implementing Genomics in Practice
MDHHS	Michigan Department of Health and Human Services
MODY	maturity-onset diabetes of the young
NHANES	National Health and Nutrition Examination Survey
NHGRI	National Human Genome Research Institute
NIH	National Institutes of Health
PEER	Platform for Engaging Everyone Responsibly
PMI	Precision Medicine Initiative

RCT	randomized controlled trial
TAPUR	Targeted Agent and Profiling Utilization Registry

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Introduction and Themes of the Workshop[1]

Although it is becoming increasingly more common for clinicians to use genomic data in their practices for disease prevention, diagnosis, and treatment, *the process* of integrating genomic data into the practice of medicine has been a slow and challenging one. Some of the major barriers impeding the incorporation of new genomic technology into clinical practice are: the difficulty of changing routine medical practices to account for the use of genetic testing, the limited knowledge of patients and providers about genomic medicine, assessing sufficient evidence to support the use of genetic tests, privacy and data security issues, and uncertainty about reimbursement (Manolio et al., 2013).

Genomic medicine programs are currently under way at several academic medical centers and large integrated health systems (Manolio et al., 2013), but it has been challenging to identify which genomic applications have robust evidence supporting their use in the clinic to improve patient outcomes (Dotson et al., 2014). With a constantly evolving evidence base, it is not unexpected that, even with the integration of successful applications, the collection of evidence could continue during genetic test implementation (see Chapter 4). Furthermore, the incorporation of genomic approaches into clinical care is taking place independently at medical centers throughout the country, and practices and health systems could benefit from structured collaboration, knowledge sharing, and an implementation

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

framework to improve the efficiency and effectiveness of practice change.

The field of implementation science may be able to provide insights concerning efficient ways to incorporate genomic applications into routine clinical practice. One definition of implementation science is "the study of methods to promote the integration of research findings and evidence into health care policy and practice"[2] (NIH, 2016). The focus of implementation science studies is to identify integration bottlenecks and optimal approaches for a given setting and ultimately to promote the uptake of research findings (WHO, 2014). The overarching goal of the field is to create generalizable knowledge that can be applied across settings to achieve sustained health improvements (Madon et al., 2007). Implementation research can be applied to a variety of fields and issues pertaining to education, civil and criminal justice, social welfare, and child welfare. The tools and approaches of implementation science could help make it possible to more efficiently incorporate genomic advances into common clinical practice.

To explore the potential of implementation science to improve the integration of genomics into medicine, the Roundtable on Translating Genomic-Based Research for Health held a workshop in Washington, DC, on November 19, 2015, titled Applying an Implementation Science Approach to Genomic Medicine.[3] The workshop brought implementation scientists together with clinicians, payers, community engagement experts, and health systems leaders who have an interest in genomic medicine. It has been difficult to bridge the gap between discoveries in genomics and positive population health outcomes, observed workshop co-chair Greg Feero, associate editor of the *Journal of the American Medical Association*, and implementation science may offer an opportunity to close that gap and provide cumulative knowledge that can be adopted and adapted so that "institutions are not forced to reinvent the wheel at each site every time."

During the workshop, speakers and participants discussed the challenges and opportunities of integrating genomic advances into the clinic through the lens of implementation science, and by doing so they are "ready to talk about implementation in a new way," according to Roundtable co-chair Sharon Terry, president and chief executive officer of Genetic Alliance. The specific workshop objectives are provided in Box 1-1.

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[2]See http://www.fic.nih.gov/researchtopics/pages/implementationscience.aspx (accessed February 26, 2016).

[3]The workshop agenda, speaker biographical sketches, statement of task, and registered attendees can be found in Appendixes A, B, C, and D, respectively.

BOX 1-1
Workshop Objectives

- To elucidate options for accelerating the pace of implementation and evidence generation in genomic medicine by convening medical implementation science experts with stakeholders representing the continuum of genomics translational research.
- To discuss possible strategies for reaching and engaging diverse populations when introducing genomic medicine into practice.
- To explore the challenges, successes, and best practices that facilitate rapid and appropriate translation of genomic knowledge from early discovery to population health.

OVERVIEW OF THE WORKSHOP

Implementation research is designed to "generate insights and knowledge about implementation processes, barriers, facilitators, and strategies," explained Brian Mittman, a research scientist at Kaiser Permanente Research. Workshop speakers examined issues that pertain to advancing genomic medicine, including engaging diverse audiences in genomic medicine, gathering evidence during implementation, and using genomic medicine to improve population health. The underlying question throughout the workshop was, "How can implementation science help to address these challenges?"

Following each session's presentations, a panel of five reactants offered reflections on and extensions of the presenters' comments from the perspectives of a clinician, a payer, an implementation scientist, a patient advocate, and a health disparity expert. The reactants' remarks are incorporated throughout this summary to recap some of the most important themes emerging from the workshop.

Engaging Large and Diverse Audiences

One major issue concerning the implementation of genomic medicine is determining which methods will encourage widespread participation from minority or disadvantaged populations. Genome-wide association studies (GWASs) have expanded the understanding of a broad spectrum of human traits and diseases, but many of these studies include relatively small numbers of samples derived from minority groups (Coram et al.,

2015). Small sample sizes from minority populations could result in gaps in the evidence base used in genomic research—and subsequent inequities in clinical care.

Systematic efforts are under way to engage diverse populations in genomics research by enhancing communication and building trust (NHGRI, 2016). Such engagement can help ensure that the implementation of genomic medicine fits the needs of specific populations and also fits within the local context (Joosten et al., 2015). Introducing genomic medicine at both large academic health centers and small community-based practices will be important for reaching diverse patient populations. Community engagement can help reveal gaps in an implementation strategy and provide critical evidence needed to fill those gaps (see Chapter 3). In addition to community engagement, consistent financing strategies and efforts to improve genomic literacy among multiple groups (including clinicians, payers, and patients) could all promote the inclusion of minority and underserved populations in genomic research and medicine.

Gathering Evidence During Implementation

Synthesizing robust evidence is another issue that is important for the integration of genomic innovations into clinical practice. Lengthy time periods between discovery and clinical uptake can be attributed, in part, to a linear research approach which encourages stepwise progression from evidence building to clinical research to implementation research (Glasgow et al., 2003). However, evidence building and clinical research can be done in parallel with implementation research, in what is referred to as hybrid effectiveness-implementation studies (see Chapter 4). The examination of case studies of rapid and successful implementation of genomic applications could yield valuable information about how to optimize the uptake of new genomic medicine approaches.

Implementation Science and Population Health

The integration of genomics into clinical care has the potential to improve public health at the population level, to expand our understanding of human diseases, and to increase genomic literacy. Programs run by state health departments, such as the Public Health Genomics Pro-

gram in Michigan,[4] can be examples of how the adoption of genomic applications has the potential to affect population health (see Chapter 5). Certain genomic applications, if implemented in the proper subset of the population, have the ability to save lives, prevent disease, or improve the quality of life for many patients (Green et al., 2015). Implementation science may help to build a common framework and best practices for integrating evidence-based genomic applications into population health programs. Designing a framework and identifying best practices for implementation involving a diverse group of stakeholders could result in a successful plan for incorporating genomics into practice.

ORGANIZATION OF THE WORKSHOP SUMMARY

Immediately following this introductory chapter, Chapter 2 provides an introduction to implementation science research, with a special focus on its goals, methods, and approaches. The chapter also includes background on the distinctions that set implementation science apart from related fields. Attention is paid to the barriers to implementation, evidence generation during implementation, and gaps in implementation research as they relate to genomic medicine.

Chapter 3 examines specific methods for engaging a large and diverse patient population in the early stages of implementation, where information gathered can be useful for genetics discovery efforts. The case studies of implementation presented in Chapter 3 involve a large regional health care system, a genomic research network in Québec, and a program aimed at enrolling greater numbers of underrepresented minorities into research. This chapter also addresses the issue of identifying the most appropriate time to introduce implementation science into the translation process.

Chapter 4 explores models for gathering evidence as a new technology or practice is being introduced into routine care. The evidence gathered during implementation can include measures of the knowledge and skills of providers, patient acceptance, external incentives, and health outcomes. This chapter features a case study on a proprietary program for health care providers that offers easily accessible information on cancer treatments and clinical trials. In addition, Chapter 4 examines the rap-

[4]For more information on the Public Health Genomics Program in Michigan, see http://www.michigan.gov/mdhhs/0,5885,7-339-73971_4911_4916_47257---,00.html (accessed February 23, 2016).

id adoption of a novel genomic technology and the benefits and disadvantages of its speedy implementation.

Chapter 5 focuses on effective strategies and infrastructure that can facilitate the implementation of genomic medicine equitably across the population. This chapter describes a multifaceted statewide genetics plan as well as a pan-Canadian biobank that is in the process of expanding from longitudinal cancer studies to other disease fields. A bottom-up approach to improving diabetes diagnoses is also presented, highlighting the value of evidence gathering in strengthening the implementation process.

In Chapter 6, the value of using implementation science in genomics is considered, particularly as it relates to addressing health disparities, improving genomic literacy, and financing genetic approaches in clinical care. Potential ideas from individual speakers for actionable next steps are laid out in Chapter 6.

2

Implementation Science: Methods and Approaches

Important Points Highlighted by Individual Speakers

- Implementation science can accelerate the translation of basic and clinical genomic research findings by assessing how health care professionals and organizations behave and then applying that knowledge to the process of changing routine clinical practice. (Mittman)
- Considering the setting for implementation (e.g., large health care system, community health center) on the front end of innovation could support translation by encouraging early thinking about how a discovery could affect a system. (Chambers)
- Large, multifaceted, stakeholder-developed strategies are needed to address the various constraints to implementation, such as insufficient provider knowledge and time, incomplete evidence, inconsistent financing, and a lack of systems support. Comprehensive strategies are useful because the more commonly used quality improvement approaches to implementation address only a small subset of quality problems and may not be sufficient for successful integration. (Mittman)
- Researchers often consider delaying implementation because they are working with an incomplete evidence base; however, by designing hybrid approaches that combine effectiveness and implementation research, it could be possible to move ahead with implementation as the evidence base is still expanding. (Mittman)
- Clinical researchers have the opportunity to generate evidence at all stages of implementation; however, it is important to recognize that there are conditions under which certain applications should not be implemented, such as when there is a poor fit between an intervention and the setting in which it is being delivered. (Chambers)

The objective of implementation science is to incorporate new findings into clinical practice. On average it takes 17 years to convert just 14 percent of original research into benefits for patients, said David Chambers, deputy director for implementation science at the National Cancer Institute (Balas and Boren, 2000). Furthermore, the 17 years does not include how long it takes to develop and perform the research. This chapter describes the goals and approaches of implementation science and identifies areas where the field may provide benefits to genomic medicine.

THE GOALS OF IMPLEMENTATION SCIENCE[1]

In the progression of discoveries from basic research to clinical research and from clinical research to improved health outcomes and processes, implementation science focuses on the latter half of the process, known as Type 2 translation (see Figure 2-1), said Brian Mittman, a research scientist at Kaiser Permanente Southern California. However, Mittman went on to note that those working in implementation science have tried to minimize use of the word "translation" in describing their work, partly because of confusion about different forms of translational research.

Mittman defined implementation science as "the scientific study of methods to promote the systematic uptake of research findings and other evidence-based practices into routine practice and, hence, to improve the quality and effectiveness of health services. The field of implementation

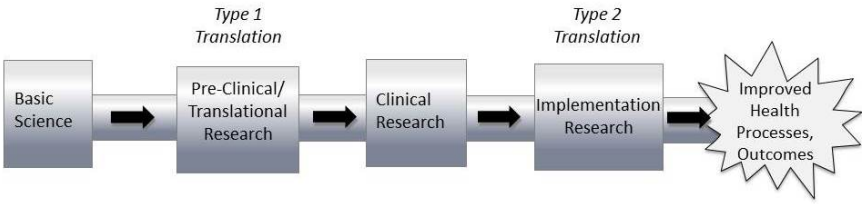

FIGURE 2-1 A depiction of the translational research continuum showing how basic science can potentially result in improved health processes and outcomes. Implementation research focuses on the latter half of the process known as Type 2 translation.
SOURCE: Brian Mittman, National Academies of Sciences, Engineering, and Medicine workshop presentation, November 19, 2015.

[1]Additional background reading on implementation science is available in Appendix E.

science includes the study of influences on health care professional and organizational behavior."

Mittman identified three major aims of implementation science as they pertain to health care:

- To generate reliable strategies for improving health-related processes and outcomes and to facilitate the widespread adoption of these strategies.
- To produce insights and generalizable knowledge regarding implementation processes, barriers, facilitators, and strategies.
- To develop, test, and refine implementation theories and hypotheses, methods, and measures.

"The goal of research in implementation science—and this applies to other complex interventions as well—should not be to determine whether an implementation strategy is effective or not," Mittman said. Rather the goal should be "to understand how [the strategy] works and to ultimately provide guidance in adapting, modifying and customizing it by [providing] an understanding of its mechanisms of action so [the strategy] can be made to work more effectively." In some cases, he said, the implementation setting can also be modified to increase the likelihood of success—for example, by strengthening institutional leadership or modifying culture or mindsets.

Work in implementation science is published under a number of different identifiers, including knowledge transition, translational research, research utilization, knowledge utilization, knowledge-to-action, knowledge transfer and exchange, technology transfer, and dissemination research. One controversy within the field, Mittman said, is whether to coalesce around a single set of terms, in part to gain greater legitimacy and support for this work, or to support the existing multitude of terms. One potential problem with the latter approach, he said, is that it might lead to confusion among leaders at health care systems, who may think that they already have implementation science programs underway when in fact they are using the approaches of quality improvement, or another related field.

There are key differences between implementation science and such fields as quality improvement, Mittman said. Quality improvement commonly targets specific local quality problems via rapid-cycle iterative improvement. Implementation science generally seeks to develop and rigorously evaluate fixed implementation strategies to address implementation gaps across multiple sites. In this respect, the goal of im-

plementation science is to develop *generalizable* knowledge. Because of these differences between the two fields, Mittman said, there are opportunities for synergy as well as opportunities—many of them unfortunately missed—for those in both fields to learn from their colleagues. Another important distinction is between implementation science and comparative effectiveness research, specifically their goals, methods, measures, and outcomes. Comparative effectiveness research involves the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition or to improve the delivery of care (IOM, 2009).

One unique aspect of implementation science is its focus on the ways in which interventions can and cannot be replicated across settings, such as integrated health care systems, academic medical centers, and community-based clinics. The findings of implementation science generate "insights into constraints, into some of the core principles that would allow us to select from a mix of implementation interventions, deploy them in different ways, and adapt them," Mittman said. In complex organizations, *function* is the underlying need that is addressed by an intervention, whereas *form* is the way that an intervention is operationalized. "For most of these implementation problems," Mittman said, "there's a relatively constant list of functions that need to be fulfilled. But the exact form that those implementation strategies or components would take—the way we provide for patient education support or clinician education, or the way that we achieve conducive professional norms—those strategies are likely to differ across sites."

INSIGHTS ON THE ADOPTION OF NEW CLINICAL PRACTICES

Implementation science has generated several key insights concerning the adoption of new clinical practices, Mittman said. For example, Damschroder and colleagues published a Consolidated Framework for Implementation Research (CFIR), which offers an overarching classification system to promote implementation theory development, and verification (Damschroder et al., 2009). The CFIR is composed of a multitude of factors that have been shown to influence implementation processes and outcomes, including the characteristics of an innovation, the inner setting, the outer setting, the individuals who deliver care or facilitate implementation, and the implementation process. There are instances when an evidence-based, practice-changing strategy will not succeed

because the external regulatory environment, social environment, or fiscal environment are not conducive to change, Mittman said. "Implementation science is not a matter of focusing on one or two factors but, instead, taking into account the full spectrum of influences on clinical practices and attempting to both understand these influences [and] leverage the influences."

Clinical practices are highly stable and slow to change, a phenomenon that is sometimes referred to as *clinical inertia*. In many ways, the stability of health practitioners is highly appropriate, Mittman said. Clinicians are often hesitant to change the way they practice medicine because they are used to contradictory evidence in the literature, he said. But he added that interventions typically are not based on the results of single studies but rather on systematic reviews, clinical practice guidelines, and other stable and strong bodies of evidence. Researchers at the University of California, Los Angeles, developed a multicomponent cancer genetics toolkit that attempted to address many of the constraints that cause clinical inertia (Scheuner et al., 2014). The goal of the toolkit was to facilitate the collection and use of cancer family histories by primary-care clinicians. There were several distinct components within the toolkit, including a continuing medical education–approved lecture series, patient and clinician information sheets, a reminder embedded in the electronic health record system, patient questionnaires, and a practice feedback report. According to the authors, this multilevel approach resulted in increased clinician knowledge regarding cancer genetics, an increase in cancer family history documentation, and higher rates of patient referrals to genetic counselors.

Another insight from implementation science is that practices and settings are highly heterogeneous. Implementation strategies need to be multifaceted in order to attend to the numerous influences and constraints on clinical practice, Mittman said, and "simple practice change strategies are not sufficient."

Finally, Mittman pointed out that supportive norms are needed to enable practice change. Professional norms and external expectations, including the expectations of patients, can drive practice changes, just as improvements in knowledge and skills can. "Physicians are well aware of the fact that there are many opportunities to improve care. They have limited time. They allocate their time and attention to what is often referred to as the squeaky wheel. When we have performance measures in place, when we have other strategies that direct the attention of clinicians

and staff to specific problems, there's a great likelihood that they will change."

APPLYING IMPLEMENTATION SCIENCE TO GENOMICS

The intersection of genomics and implementation science is a particularly ripe area for exploration, Chambers said. There are many open questions with regard to the sustainability of evidence-based practices in a changing context, and the adaptability and evolution of evidence-based practices over time. "Most of the scientific community would agree that we certainly have reached a point where there are [genomic] applications that ought to make their way into regular use," Chambers said. For example, the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) working group, overseen by the Centers for Disease Control and Prevention, has developed a systematic process for assessing evidence regarding the validity and utility of rapidly emerging genetic tests for clinical practice. EGAPP has identified a number of "Tier 1 findings," which are classified as genomic applications with sufficient evidence to support their use in the clinic (Teutsch et al., 2009). One example of a Tier 1 finding, Chambers said, is screening within the colorectal cancer population for Lynch syndrome. Lynch syndrome is a hereditary disposition to developing colorectal cancer and certain other malignancies due to a mutation in a mismatch repair gene (EGAPP Working Group, 2009). Clinicians need to be thinking about delivering the initial test for Lynch syndrome to high-risk individuals along with the ongoing screening and monitoring needed to manage someone with high risk, Chambers added. This will require effective coordination of the test and the cascade of actions that should follow in order to optimize care for carriers and their family members.

Similarly, there is a strong evidence base linking specific BRCA1 and BRCA2 mutations to an increased risk for breast cancer and other malignancies (Campeau et al., 2008). Effective implementation requires the identification of mutations at the population level, effective scaling up to family members, and the establishment of screening, monitoring, and preemptive treatment, Chambers said.

Stakeholders may also want to carefully consider the demand for new genetic tests before trying to implement them in clinical care, Chambers said. Demand depends on having informed patients who are able to make and articulate their decisions and also on whether a new test fits into a clinical pathway where testing is the norm, he said.

Available Resources

An increasing number of resources are available for those interested in pursuing implementation science, including training programs, research infrastructures, improved measurement tools, and other tools to link research with practice and policy. Annual conferences on the topic bring together more than 1,000 people, many of whom have committed to implementation science as a career, Chambers said. The journal *Implementation Science* is an open-access, peer-reviewed online journal which publishes research that is relevant to the scientific study of methods to promote the uptake of research findings into routine health care in clinical, organizational, or policy contexts.

Chambers said that those interested in implementing genomics into clinical practice can learn a great deal from other disciplines that face similar issues. The Global Implementation Society, part of the larger Global Implementation Initiative, was designed to unite implementation experts across fields to define, support, and expand professional roles related to implementation in human service organizations and government systems.

POTENTIAL GAPS IN IMPLEMENTATION RESEARCH

A variety of research gaps exist in the implementation science pipeline. One such gap is root cause analysis, especially as it applies to diagnosing potential problems during the implementation of new clinical practices. As Mittman observed, often "we take an implementation strategy or quality improvement program that has been shown to be effective elsewhere and we apply it to a new problem, which is in some ways similar to taking a medication that has been shown to be effective for reducing severity of headache and applying that to a set of patients with an unrelated condition." Those integrating new clinical practices need to diagnose the implementation gaps such as insufficient system support or misaligned financial incentives, before they develop an implementation strategy and begin to evaluate that strategy, said Mittman.

Rigorous randomized controlled trials (RCTs) are generally preferred by academic scientists and peer reviewers. However, in implementation science, "RCTs tend to be very artificial, have very low external validity, and oftentimes not very much value," Mittman said. "Many of the insights that we need to generate regarding implementation barriers, pro-

cesses, and strategies are probably more easily obtained from observing and studying natural experiments. We need much more observational implementation research and probably a bit less interventional implementation research," he added.

Even when large and expensive RCTs are conducted, they may show that an intervention did not succeed in changing clinical practice, Mittman said. Small pilot projects at a single site can often provide important information about implementation barriers that avoids the burden of large and costly studies at multiple sites, he added.

Given the challenges of root cause analysis and study design, the best approach to implementation research is to develop a diverse portfolio of studies, including efficacy-oriented implementation studies that use grant funds to hire staff to provide monitoring and technical assistance, and other effectiveness-oriented studies "where we as the implementation research team [take a step back] and allow the system to essentially do its thing," Mittman said.

What May Be Learned from Implementation Research

In an effort to identify which health interventions can fit within real-world public health and clinical service systems, the National Institutes of Health (NIH) is conducting dissemination and implementation research.[2] Chambers noted that the NIH defines dissemination as "the targeted distribution of information and intervention materials to a specific public health or clinical practice audience" and implementation as "the use of strategies to adopt and integrate evidence-based health interventions and change practice patterns within specific settings" (Lomas, 1993). Much of the current implementation research has focused on the effectiveness of different implementation approaches, methods development, training systems for providers, financing and policy changes, and emerging approaches such as learning collaboratives and the use of technology as a driver of dissemination and implementation.

The NIH has room to improve its methods for dissemination and implementation Chambers said. "We need to do a better job of more active and more effective dissemination of the information that our science generates," he said. "And then we need to do a better job of figuring out

[2]For further information about implementation science resources from the NIH, see http://www.fic.nih.gov/researchtopics/pages/implementationscience.aspx (accessed February 22, 2016) or http://cancercontrol.cancer.gov/is/index.html (accessed February 22, 2016).

how we implement change and how we use strategies to adopt and integrate effective health interventions."

The core of implementation research consists of implementation strategies, implementation outcomes, and service outcomes, Chambers said. Implementation studies often focus on questions such as:

- Is implementing a particular practice feasible within a given setting?
- Is the practice acceptable to clinicians, to patients, and to systems?
- What are the costs associated with the innovation?
- Can the practice be sustained over time?
- What are the levels of fidelity or quality that are needed to ensure good outcomes?

The NIH has a number of standing program announcements on dissemination and implementation research, which to date have yielded over 140 projects cutting across 16 institutes and centers, Chambers said. The NIH recognized that across many disciplines, researchers and clinicians were struggling with the challenges of implementation such as feasibility, provider readiness, sustainability, financing, and quality, Chambers said.

POSSIBLE OBSTACLES TO IMPLEMENTATION

Several obstacles to implementation were described by Mittman, particularly the challenge of handling the vast amount of information available (see Box 2-1). For example, in the past, the volume of clinical knowledge was limited enough that individual physicians could go through a period of training and apprenticeship and obtain most of the knowledge required for the job. Today, however, the body of required knowledge has grown so large that clinicians cannot keep it in their minds, and a much larger spectrum of factors influence clinical practice, Mittman said. "It's no longer a matter of changing physician practices through continuing medical education; it's now a matter of trying to influence all of these different factors, levers, or constraints." As a result of this added complexity, quality improvement strategies that focus on just a few causes of conservative practice and instability typically are not sufficient, Mittman remarked. Instead, large, multifaceted, stakeholder-engaged, partner-oriented strategies are needed to address all of the constraints, he said.

BOX 2-1
Possible Challenges to Implementation (as presented by Mittman)

- Insufficient information and guidance for reaching clinical decisions
- Lack of time for providers to effectively implement
- Providers receive too much information[a] to implement
- Evidence not accepted as legitimate
- Implementation gaps not recognized
- Misaligned financial incentives
- Insufficient staff or systems support
- Lack of external pressure and expectations

[a]There may be inconsistent explanations offered to explain slow or limited adoption of research findings and evidence-based practices into clinical care. Some observers note that clinicians lack sufficient information for clinical decision making, while others note that clinicians face the opposite—an "information overload"—and have too much data to process for making decisions.

Another obstacle to implementation that Chambers cited is that many innovators do not think carefully about the fit between the things they are developing and the audiences and systems that are required to implement those innovations. These issues need to be considered on the front end of innovation, he said. For example, even if a genomic test identifies the optimal treatment for an illness and can reduce the risk for health problems, the mere existence of a test does not ensure its use. In this instance, if only half of insurers choose to cover that test, only half the systems that incorporate the test train their clinicians to use it, only half the clinicians trained actually use it in practice, and only half of their patients get tested (assuming perfect access, testing, and follow-up), only about 6 percent of patients will benefit. And these assumptions are optimistic, Chambers said. The return on investment could come from tests making their way through this cascade of obstacles into use.

EVIDENCE GENERATION DURING IMPLEMENTATION

In some cases, a technology or practice is implemented in practice after evidence has been gathered, but in other cases evidence needs to be gathered as a technology is being introduced into care (see Chapter 4). This raises a dilemma, as Mittman pointed out. "What do we do about a clinical practice for which the evidence base is not quite as strong as we

would like it to be but it addresses an important clinical question for which we don't have better alternatives? Should we proceed to begin to implement that practice even though the evidence is not solid, or do we continue to study clinical effectiveness and only after 5 to 10 years of that type of research move into implementation?"

One potential answer to this dilemma is hybrid approaches that combine effectiveness and implementation research. Blended effectiveness–implementation studies may provide benefits such as accelerated translation, more effective implementation strategies, and higher quality information for researchers and decision makers (Curran et al., 2012). In addition, the hybrid studies offer a way for those who are not necessarily interested or do not feel qualified to conduct implementation studies to facilitate the adoption of their work, Mittman said.

Approaches to implementation science have changed over time in ways that are helpful for evidence generation, Chambers said. Innovation is no longer viewed as a strictly linear process progressing from basic research to clinical research and, ultimately, to community practice. Despite widespread recognition of the existence of feedback in an otherwise linear process, it was often assumed that there needed to be a complete evidence base before the innovation could be implemented in practice. However, the evidence base does not need to be optimal prior to starting to implement, he said. The challenge for the future is recognizing that researchers have an opportunity to generate evidence at all stages of implementation, and adapting to incoming evidence in real time, Chambers said.

UPDATING THE THINKING ABOUT IMPLEMENTATION SCIENCE

There are several outdated assumptions about implementation science that could be superseded by new knowledge, Chambers said. First, evidence-based practices are not static and instead are constantly changing, as is the system in which those practices are being implemented. Implementation does not proceed one practice or test at a time, and consumers and patients are not homogeneous. Finally, choosing to de-implement unsuccessful practices or not to implement an evidence-based practice is not necessarily irrational. "There are all sorts of legitimate reasons why things are not implemented, and we need to understand those," Chambers said. "We need to be thinking about the fit between our testing, the fit between our interventions and where they're delivered,

and how they fit into the workflow as well as the needs of the population that we're trying to serve."

3

Engaging Large and Diverse Populations for Analysis

Important Points Highlighted by Individual Speakers

- Characteristics of large health care organizations such as their population size, extensive data collections, and existing infrastructure make these organizations useful systems in which to carry out implementation research. (Faucett)
- The implementation of genomics in clinical care can be accelerated by having health economists, ethicists, and regulatory personnel work in parallel with researchers, rather than in sequence, to effectively and efficiently change practice. (LePage)
- Many researchers underestimate the amount of time, funding, and personnel required to engage minority populations in research. Recruiting racial and ethnic minorities to participate in genomic research requires specialized expertise early on in the study design and additional efforts for recruitment, retention, and proper clinical support following the release of test results. (Wilkins)
- Engaging with implementation scientists early in the translational process can increase the likelihood that new genomic approaches will be adopted and adhered to in the clinic. (Mittman)

One potential source of data for genomic medicine implementation research is cohorts that have been assembled for discovery purposes.[1] This chapter examines a genomics biobank operated by a large regional

[1]For more information and background reading on large genetic cohort studies, see Appendix F.

health care system, a genomics research network in Québec, and an innovative program designed to boost racial and ethnic minority participation in genomics research.

A GENOMICS-FOCUSED BIOBANK

The Geisinger Health System, based in central Pennsylvania and southern New Jersey, is an integrated health services organization that has made a commitment to genomics and personalized health care, said Andrew Faucett, the system's director of policy and education. Geisinger is working to make the system a learning health laboratory characterized by a continuous cycle of integrated innovation, implementation, assessment, and reengineering in all aspects of its clinical and research mission. To do so, Geisinger is engaging and partnering with its patients and others in the community.

The Geisinger Health System serves a geographic area with a large, stable population of more than 2.5 million people and has more than 700,000 active patients, including many families of three or more generations, Faucett said. Geisinger has a strong and trusting relationship with its patients, he added. Having used the same electronic health record (EHR) system since 1995, the system has compiled comprehensive clinical data.

Geisinger is currently discussing options for storing genomic data within the EHRs. Genomic data in EHRs could be useful in generating automatic notifications of family members, Faucett said, and the EHRs could be provided to children and grandchildren. From a care perspective, Faucett said, it would be much easier if a patient could say something such as "I know my uncle has a Lynch Syndrome mutation" and the clinician could then simply identify the mutation and offer the patient testing instead of asking the patient's uncle to return a signed release. "The more we can automate it with permission, the easier it will be," he said.

The Geisinger patient population does not have much racial or ethnic diversity, Faucett said, but it does have a great deal of socioeconomic diversity. Central Pennsylvania has one of the highest poverty rates in the United States, and access issues often arise because many people live in rural communities. For that reason, he said, care close to home is part of the Geisinger model. Roughly half of Geisinger patients do not have dependable Internet access in their homes, he said, and they depend much

more on smartphone access. Those patients involved in genomics studies need quick access to information, he said, because they can very quickly become extremely concerned once they learn of their test results. "You have to have folks in place who can quickly intervene" and talk through the results with them, Faucett remarked.

Outreach

A major component of the Geisinger research vision, Faucett said, has been an online genomics data system and biobank known as MyCode®.[2] One of the goals of the MyCode biobank is to help researchers gain a better understanding of the impact of genes on human health and disease states. Additionally, Geisinger hopes that information from this resource will assist in the development of tailored therapeutics, bringing its clinicians and patients one step closer to precision medicine. Community engagement has been an essential element of developing and operating the MyCode system, Faucett said. In 2006, prior to launching MyCode, Geisinger organized focus groups from the general patient population to explore the idea of a genomics database. Focus group discussions were centered on pharmacogenomics, recessive carrier status, increased risks for both preventable and treatable conditions as well as conditions that are not preventable and treatable, and genetic changes that are not currently understood. The Geisinger system provides additional outreach to the community through regular updates in the form of newsletters, and it encourages employees to participate in MyCode.

Geisinger is very interested in engaging families in preventive genomic medicine, Faucett said, in part because many of its patients come from large families. Moving forward, the system is considering bringing on more genetic counselors, reaching out to large families at reunions, and using online venues to "get the word out in a large volume without having to see each person individually."

Return of Results

Geisinger also convened an additional six focus groups in 2012 prior to implementing procedures regarding the return of research results. One major outcome from the 2012 focus groups was the realization that par-

[2]For more information on MyCode, a biobank program within the Geisinger Health System, see http://www.geisinger.org/for-researchers/partnering-with-patients/pages/mycode-health-initiative.html (accessed February 22, 2016).

ticipants wanted *all* results returned to them, Faucett said. "They were not comfortable with [results] going just to the health care provider, which is often what we want to do as a medical practitioner," he said. The participants were fine if the results went to the health care provider first, but they wanted to have access to their own results, he explained. As the system is currently set up, providers receive the results about 5 days before system participants.

Participants receive information on genetic variants that have been identified as "actionable" by the American College of Medical Genetics and Genomics (ACMG), plus a few others that are not included on the list (Green et al., 2013). Geisinger does not currently examine pharmacogenomics variants because it is not equipped to return the results of these findings. Clinicians are willing to use pharmacogenomics if the data are already in the record, Faucett said, but they are not currently willing to order a test and wait to make a decision. "Our long-term goal is that this type of information will be available on every patient," he said.

Faucett characterized the system's work in genomics as a fusion between an academic and a business approach. Geisinger was interested in performing exome sequencing as a way of understanding the genome, but as a health care institution it also felt that it was unethical to have that information and not give something back to the patients. "That's why [Geisinger] took the ACMG list and said, 'Let's return this, and let's study it as we return it,'" Faucett said. There are economists involved with this work, but it is not currently classified as a formal implementation study. "We need more people and more money to do it that formally, but we're trying to look at all of those issues."

The return of results to patients is being modified based on real-time feedback. The overall intent, Faucett said, is to start with national recommendations and tailor those recommendations from within the system's population. "It needs to be tweaked for each [Geisinger] location," he remarked, reiterating one of the goals of implementation science which is to adapt and refine practice change strategies based on the characteristics of a particular setting.

Participants in the 2012 focus groups also requested educational materials on genomics for clinicians and for patients. Focus group participants had a lot of respect for their clinicians; however, Faucett said, they requested educational materials and an expert support system for providers and patients. Patients were comfortable with results being put in their EHR and liked the idea that their records are available throughout the system.

Engaging the Community

There is an ethics advisory committee in place for the MyCode program which includes four nationally recognized ethics experts and four local patients. The committee has worked diligently on the consent form which provides guidelines for recontacting patients, collecting longitudinal samples, returning results, placing results in the EHR, and online consent. The consent has been repeatedly revised, Faucett said. "It's a process between the researchers, the institution, and the institutional review board. Clearly, back in 2006 everyone was terrified of genetic results; no one wanted them in the electronic medical record. . . . Now our philosophy is that returning results should be the standard practice." Progress has been gradual but steady, Faucett said, and they are becoming more comfortable with the precision medicine movement.

Engaging the providers is also important, Faucett continued. Geisinger has taken a multifaceted approach to engaging providers, including

- An oversight committee that handles the return of results
- Frequent presentations to clinical and administrative leaders across the system
- A genetic counselor who networks with physicians and administrators
- Regular symposia that provide information on specific genomic test results
- Short courses for each of the conditions for which results are being returned
- Fact sheets and other educational materials for providers

The consent rate for MyCode is currently at 85 percent, with 98,000 individuals currently in the biobank and 88,000 of those allowing the return of results, Faucett said. Through a new partnership with Regeneron Pharmaceuticals, Inc., Geisinger is working to perform whole-exome sequencing. Thus far, whole-exome sequencing has been performed on 52,000 participants, with 44,000 of those agreeing to the return of results. The enrollment goal for the whole exome sequencing study was recently increased to 250,000 patients.

GENOMIC RESEARCH IN QUÉBEC

With a population of about 8 million, Québec spent about $45 billion on health care in 2012, representing approximately half of the province's budget, according to Marc LePage, president and chief operating officer of Génome Québec. Per capita health care expenditures in Québec are the lowest of any province, so Québec has been successful at cost containment, LePage said, but the province has not been particularly adept at launching new innovations. To remedy this deficiency, Génome Québec was launched in 2000 and is one of six regional genomics centers that are part of a national program called Genome Canada. The mission of Genome Canada is to develop and apply genomics-based technologies that provide social and economic benefits for the Canadian population. Génome Québec has faced several challenges in its quest for accelerating the discovery of new genomic applications, which LePage described, together with solutions to overcome these barriers.

Establishing a Biobank to Foster Research and Innovation

In partnership with McGill University in Montreal, the Génome Québec program has an innovation center which includes a sequencing platform, a clinical genomics facility, and several broadly distributed population cohorts. One arm of the program, known as the CARTaGENE Biobank, is one of five regional population health projects that are part of the Canadian Partnership for Tomorrow Project (CPTP). CARTaGENE serves as a long-term bioresource that is collecting biological samples and data that are representative of the genomic diversity of Québec's population. CARTaGENE was established with the goal of collecting more complete information about genes, environment, and lifestyle across the population and subsequently making that information easily accessible to researchers. During its first recruitment phase, CARTaGENE enlisted 20,000 participants. Participants range in age from 40 to 69 years old, and samples are collected at 12 clinical sites in four urban centers, LePage said. The data available for this cohort include answers to health questionnaires, biological samples, (including blood, saliva, urine, and cell samples), physical and clinical measures, genealogies, and nutrition and environment surveys. A second and ongoing recruitment phase has a goal of enlisting another 20,000 participants of the same ages. CPTP has been quite successful, LePage said, and it now has samples from close to 300,000 participants (Borugian et al., 2010).

To encourage innovative discoveries within the realm of genomic medicine, Génome Québec organized a Genomics and Personalized Health Competition. The request for applications was specifically designed to include a requirement for outlining implementation strategies, LePage said. For example, researchers who applied for the competition were asked to provide an implementation roadmap as part of their proposals. Competition winners received funding to complete their projects. The winning projects, now underway, cover a wide array of fields including genomics drug discovery, breast cancer detection strategies, prenatal testing, and the development of tools to advance diagnosis and treatment. With a solid foundation in basic research, Génome Québec has also become involved in technology-focused genomics and clinical applications, LePage said.

Garnering Support from Clinical Leadership and Other Challenges

Part of Génome Québec's mission is to maximize the socioeconomic impact of genomics innovations.[3] Initially Génome Québec experienced difficulty in gaining support from government leaders such as the Minister of Health and Social Services, LePage said. However, after observing the program's success, Québec's Ministry of Health has undergone a change of perspective, he said, and now seeks to shape rather than resist genomic initiatives. This positive change also occurred in the regulatory sphere where internal expertise at Génome Québec was initially lacking but has now been bolstered so that regulators can do an informed review on genomics applications, LePage said.

One major change that has taken place is that projects funded by Génome Québec are now often being led by clinicians rather than fundamental scientists, LePage reported. Health economists, ethicists, and regulatory personnel are working in parallel rather than in sequence to speed up implementation. The focus of the projects has been on deliverables and outcomes rather than on processes and methods, LePage said. "We're starting with the clinical problem and working back."

The chief executive officers of health care systems would really benefit from hearing this dialogue, observed Geoffrey Ginsburg, the roundtable's co-director and the director at the Duke Center for Applied Genomics & Precision Medicine. Ginsburg went on to stress the importance of engaging experts in implementation science together with

[3]For more information on the mission and activities of Génome Québec, see http://www.genomequebec.com/en/who-we-are.html (accessed February 23, 2016).

leaders of health care systems to leverage the principles of implementation science.

Génome Québec is finding it challenging to align its databases and clinical infrastructure, LePage said. Génome Québec is trying to unite those entities now, in part through data harmonization and coordination of best practices across the portfolio. "We haven't got it solved, but we are working on it," he said. For now, genomic sequencing is only offered as part of research projects and not universally across the board, and program leaders are still trying to decide if universal sequencing is advisable. A current challenge is to decide whether sequencing a subgroup might yield information of clinical value, LePage said.

Effective communication with the public about genomics research and implementation has been a challenge for Génome Québec, LePage said. However, many people in Canada are eager to participate in biobanks, he said, because the Canadian public health care system is there when you have a problem, and as an individual you want to give something back. However, he also said that Canada is the only major country in the Organisation for Economic Co-operation and Development without a genetic privacy law, which means that confidence in the system could be damaged if privacy became a concern. In addition, genomics centers in Canada have been able to reach populations in urban centers and rural areas, but they have had trouble reaching out to people in aboriginal communities. These communities, LePage said, "are up in the north; they're isolated; they have substandard care; plus they're in a different health care system." An Institute of Aboriginal Studies exists in Canada and is working through some of the issues related to those populations, he added.

INCLUSION OF RACIAL AND ETHNIC MINORITIES

The inclusion of racial and ethnic minorities in research requires specialized expertise and extra effort, yet most researchers know very little about effectively engaging stakeholders in the research process, said Consuelo Wilkins, executive director of the Meharry-Vanderbilt Alliance and an associate professor of medicine at the Vanderbilt University Medical Center. There is very little emphasis on methods for engaging individuals in the research process during graduate-level training programs, she noted.

Vanderbilt University has developed a program called the Community Engagement Studio which is designed to enhance the planning, design, implementation, translation, and dissemination of clinical research.[4] Researchers can arrange for an advising session at the studio at any stage in the process from pre-implementation to recruitment, implementation, and dissemination. Staff members at the studio are trained to identify and recruit community members who can serve as patient stakeholders for a particular research project. Those community members learn about the research project and then provide input to the researchers, essentially acting as consultants.

Members of the Community Engagement Studio were able to advise a researcher who had been unable to recruit any African American women for a study, Wilkins said. Studio members offered guidance on how to redesign the recruiting material, on where to promote the study, and on language sensitivities involving obesity and the risk for diabetes. With this help, the researcher met the accrual goals ahead of time and had 100 percent retention in a randomized, placebo-controlled trial of a drug.

Communication involves not just recruiting members of a specific population to participate in a study but also helping them to understand and act on genetic test results, Wilkins said. According to an unpublished Vanderbilt survey cited by Wilkins, genomic literacy varies by population group, with terms such as "pharmacogenomics," "genetic testing," and "precision medicine" being more or less familiar to members of different groups. "Of Caucasians who responded, 76 percent were extremely or moderately familiar with genetic testing, but only 54 percent of African Americans were," Wilkins said.

Another critical issue in engaging minority communities in research is trust, Wilkins said. "Trust is one of the most commonly cited barriers to African Americans and other racial and ethnic minorities participating in research, but it is rarely measured." Wilkins and her colleagues have developed a conceptual framework for measuring trust in research (see Figure 3-1). When members of more affluent or dominant groups think about trust, Wilkins said, they focus on such issues as competency, honesty, and fidelity. By contrast, members of marginalized groups tend to be more concerned about whether they will be treated fairly or exposed to adverse risk. "We need to understand that and think about how we will make sure that [minority groups] are comfortable participating in the

[4]For more information on the Community Engagement Studio, see https://medschool.vanderbilt.edu/meharry-vanderbilt/files/meharry-vanderbilt/public_files/CES-Toolkit-web.pdf (accessed February 22, 2016).

work, and how will we understand what their concerns are and address them, not ignore them or pretend that they don't exist," Wilkins said.

Specific barriers to establishing trust in genomic medicine among minority groups include the eugenics movement, discrimination against people with sickle-cell trait, the potential loss of benefits or income if a genetic result is linked to a health condition, the use of DNA in the criminal justice system, and findings linked to genetics that may contradict cultural or ancestral beliefs, Wilkins said. It is important to be careful about how research findings are presented in order to ensure that the findings are seen as inclusive and not insensitive to particular populations, she added.

Strategies for recruiting and retaining minorities in research include: performing accurate feasibility assessments, staffing the program adequately with personnel experienced in engaging minorities, and devoting additional effort to retention, Wilkins said. For example, engaging populations of interest requires carefully tailored recruitment materials, appropriate language in consent forms, seeking advice on recruitment strategies, demonstrating respect and value, and offering appropriate compensation.

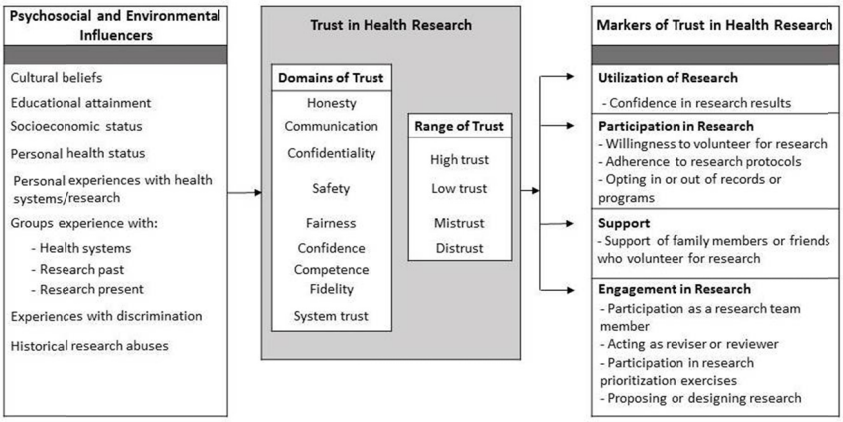

FIGURE 3-1 A conceptual framework for developing a measure of trust in biomedical research draws on psychosocial and environmental influencers.
SOURCE: Consuelo Wilkins, National Academies of Sciences, Engineering, and Medicine workshop presentation, November 19, 2015.

"Most researchers underestimate the amount of time and resources that are required to engage minorities in research," Wilkins concluded. "I often get called to help researchers when they're stuck and not able to reach their recruitment goals. Even when I come up with a plan . . . it often requires 30 to 50 percent more time and research staff to actually recruit minorities into research." And even if a particular strategy works in one group, it will not automatically translate to another group, she said.

Considering Evidence and Coverage Issues

Implementation science aims to develop generalizable knowledge, but the question is, "Generalizable to whom?" said Alexandra Shields, an associate professor at Harvard Medical School and Massachusetts General Hospital. Poor and minority communities are often missing from the evidence base, Shields said. Much of the evidence currently available is built on discovery databases drawn almost entirely from people of European ancestry (Knerr et al., 2011). "This is an issue that we need to take seriously, given the diversity that we know exists," she said. Researchers have a responsibility to investigate the source populations upon which evidence was developed, she added, and if the evidence is not based upon a diverse set of populations or patient samples, then additional studies may need to be conducted.

Shields also recommended that implementation research should be applied not just to the genetic test itself, but to the clinical care that follows after the test results are received. This includes the follow-up that ensures that the patient gets the care indicated by the test results. In that respect, implementation research could be applied to a bundled set of health care services, Shields observed. She went on to emphasize the importance of Medicaid and the Affordable Care Act coverage as being critical to the health care that patients receive. If Medicaid does not cover genomic services in a particular state, the poor may not have access to these treatments, Shields noted. A systematic analysis of the coverage of genomic services may provide valuable information about the extent to which people can access these services, she said.

Paying careful attention to the characteristics of an organization is important for designing effective implementation strategies, Shields said. For example, safety net hospitals and community health centers that serve disadvantaged patient populations may not see genomic medicine as important relative to the health needs of their populations, such as substance abuse, hepatitis C infection, and HIV infection. "We need to

strategically engage those provider groups . . . in how they conceive of genomics relative to these other health conditions," Shields said.

Timing the Thinking About Implementation

When is the most appropriate time to introduce implementation science into the translation of results into clinical applications? Patient advocates involved in the grant review process have become increasingly concerned about the impact of research, said Jane Perlmutter, president and founder of the Gemini Group and a patient advocate and cancer survivor. Involving patients and advocacy groups during the early stages of research design "has helped make sure that [researchers] at least think about the path from what they're doing to how it will impact patients," she said.

It is possible for researchers to think about implementation too early in the process, particularly if they try to push a finding into the clinic prematurely, said Brian Mittman of Kaiser Permanente Research. "Those of us who are conducting research and developing innovative practices always feel very strongly that what we've developed needs to be implemented and spread about, when in fact we should be waiting until we have a good solid body of evidence." Nevertheless, planning for implementation and implementation research does need to start very early, he added. For instance, with the development and implementation of clinical practice guidelines, the implementation team should be "involved in the process from day one, helping to develop the guidelines, helping to understand the evidence and the controversies, helping to identify ways of wording the recommendations, and providing the supporting justification," Mittman said. If this were to happen "the implementation process would be much simpler," he concluded.

4

Generating Evidence During Implementation

Important Points Highlighted by Individual Speakers

- An automated treatment pathway program can facilitate clinical research by rapidly providing clinicians with information about open clinical trials, increasing enrollment rates, and gathering data on health outcomes. (Kim)
- Clinical trials such as the Targeted Agent and Profiling Utilization Registry (TAPUR) project are designed to fit into community-based health centers, provide patients with access to drugs, and provide clinicians with knowledge about genomics-based therapeutic approaches. (Kim)
- Information collected from health care providers across a broad range of practice communities prior to the introduction of a genomic test may provide data that could predict the likelihood of successful implementation. (Kimmel)
- Cell-free fetal DNA (cffDNA) screening was rapidly integrated into clinical care and therefore is an interesting genetic test deployment to study. However, lessons could be learned from the obstacles encountered after introducing cffDNA screening, such as how to increase patient and provider knowledge about the strengths and limitations of the test. (Norton)
- Creating test-specific educational materials may help patients fully understand the information that will be generated by a particular genetic test so they are able to make well informed decisions about how to receive and access the results. (Shields)

The evidence base relied upon for deciding which genomic applications are implemented into clinical care varies in depth and lacks standards by which genetic associations are interpreted. However, it may be possible to collect new evidence as a genomics application is being implemented. Evidence collected may prove useful for assessing health outcomes, care provided, and the results of implementation. This chapter offers three case studies involving cancer, diabetes, and prenatal screening in order to explore how evidence can be collected concurrently with implementation.

PROGRAMS FOR ENROLLING PATIENTS AND TRACKING CANCER TREATMENT

Cancer treatment can be both compelling and frustrating for clinicians because of the high number of new drugs currently being approved, said Edward Kim, the Donald S. Kim Distinguished Chair for Cancer Research at the Levine Cancer Institute in the Carolinas HealthCare System. Specialists may be able to keep track of current drug approvals, but for generalists the volume of literature can be overwhelming, Kim said. Nonetheless, generalists provide much of the cancer treatment in the United States, he said. In the Carolinas HealthCare System more than 80 percent of patients are treated in community-based clinics, and most oncologists are generalists, treating patients with both hematological and solid-tumor malignancies. Generalists have a broad base of knowledge but may not necessarily be equipped to thoroughly research all of the options when multiple genomic markers and drugs are available. Oncology specialists typically have comprehensive knowledge of certain types of cancer but not all. "I spent 12 years studying lung cancer, so I can speak to pretty much any topic in non-small-cell and small-cell lung cancer," Kim said. However, if a patient asked for a recommendation on how to treat breast cancer, for example, I would need to refer them to a breast oncologist, he said. In addition to the large body of knowledge that they must keep current with, clinicians are busy, and this means limited time for patients who want to see their physicians and nurses. Kim often receives requests from clinicians within the system for more staff, but certain constraints do not allow for the addition of extra staff.

Clinical researchers face several major challenges related to evidence gathering, one of which is the low patient accrual rates for clinical trials. Estimates suggest that less than 5 percent of adult cancer patients take

part in clinical trials in the United States (Sahoo et al., 2014). Although there are exceptions every now and then, enrollment levels across the board are dismal, Kim said. As cancer clinical trials become more complex, the number of eligibility criteria increases, and thus the study enrollment rates slow down (Kim et al., 2015). Attempts to streamline eligibility criteria have led to promising proposals, but many problems remain. The American Society of Clinical Oncology (ASCO) Cancer Research Committee recently recommended that stakeholders work on developing an algorithmic approach to streamlining eligibility criteria. In addition to patient accrual challenges, clinical researchers must also plan for sample collection, regulatory approval, and communication with providers, Kim noted.

To address the challenge of low enrollment rates and to foster awareness of clinical trials, the Carolinas HealthCare System has launched a proprietary system called EAPathways. EAPathways focuses on expanding access to clinical research and new therapies. Activated in May 2015, the program alerts practitioners to clinical trials that are actively enrolling patients. The program frees up time for study coordinators so that they can focus on specific trial- and patient-related issues such as insurance and follow-up. EAPathways tracks data on trial inquiries and pathway enrollments and conducts close-to-real-time modifications of trials and pathways. Every time a patient is enrolled into a pathway, the system captures the patient's name, medical record number, and birth date. Different icons in the system represent open clinical trials, pending clinical trials, the need to collect specimens or conduct a genomics test, and clinician reminders (such as for a smoking cessation program). Generalists are not going to know about every open clinical trial, so EAPathways provides them with the information rapidly, Kim said.

EAPathways is designed to not disrupt a physician's workflow and is very quick, Kim said. Once a patient is enrolled in a clinical trial pathway, the physician receives all the required documents, including the informed consent, study sheets, calendar, and order sheets. The system is compatible with iPads and mobile phones, and inquiries about specific trials are sent directly to researchers. Furthermore, the program can be operated by support staff and does not require information specialists. Even if some physicians are not enthusiastic about using the system, their staff members have embraced it, Kim said. The system eases the workload of physicians by presenting them with information rather than forcing them to search for that material, he said. One additional feature of

EAPathways is a link to a biospecimen repository, which generates an alert to collect samples from patients once they are enrolled in a clinical trial. Overall, Kim described EAPathways as having a patient-centered approach because it minimizes travel inconveniences and promotes consistency of diagnosis, treatment, and follow-up.

The implementation of the EAPathways system has worked better for physicians employed by Carolinas HealthCare System than for physicians who are just affiliated with the system, Kim said. The Carolinas HealthCare System tries to be very aware of the latest clinical trials and enrollment in clinical trials, he said, and in return, physicians are expected to attend multidisciplinary tumor boards and participate in a monthly disease-specific section.

The Levine Cancer Institute is participating in the Targeted Agent and Profiling Utilization Registry (TAPUR) study with ASCO, the Cancer Research Consortium of West Michigan, the Michigan Cancer Research Consortium, and the University of Michigan.[1] The primary objectives of the TAPUR study are to describe the anti-tumor activity and toxicity of commercially available, targeted anti-cancer drugs and to facilitate access to those drugs for patients with advanced solid tumors, B cell, non-Hodgkin lymphoma, or malignant melanomas with a known genomic variant. Many stakeholders could potentially benefit from the design of the TAPUR study. Patients will receive access to a therapeutic agent that is targeted to the genomic profile of their tumor, physicians will receive assistance interpreting complex genomic tests, and pharmaceutical companies, payers, and regulators will have access to data regarding off-label drug use and clinical outcomes (Schilsky, 2014). The TAPUR study will initially take place at 30 clinical sites in 4 states; however, the goal is to expand the program nationally. Studies such as TAPUR are designed to fit in community-based systems, provide patients with access to drugs, minimize travel for patients, reduce the need for generalists to speculate or hypothesize, and empower physicians with knowledge and easy access to clinical trials. When clinicians can access information on clinical trials more easily, they are able to reach more diverse populations, Kim said.

One way of determining whether a cancer drug is going to be implemented rapidly is by the number of people who pursue expanded access after a drug has been approved for one indication, Perlmutter said. She is leading a patient advocacy group associated with the TAPUR trial,

[1]For more information on the TAPUR study, see http://www.tapur.org (accessed February 23, 2016).

which is designed to generate evidence on potential new cancer indications for drugs that have already been approved in one indication. Perlmutter expressed a concern that not enough work has been done to figure out how to use the evidence generated in the TAPUR trial. Currently no regulatory pathway exists to use the results of TAPUR in drug approval, she said. "If we just use the same old trials, we're not going to get [drugs] to patients fast enough, and the patients will want to keep getting them through registries as opposed to through approval, and that is going to defeat the purpose."

ENHANCING GENOMIC IMPLEMENTATION THROUGH A COLLABORATIVE RESEARCH NETWORK

> The move from considering an adoption to successfully routinizing it is generally a nonlinear process characterized by multiple shocks, setbacks, and unanticipated events. (Greenhalgh et al., 2004, p. 610)

Although this quotation comes from an analysis of innovation in service industries, it might as well have been written about genomics, said Stephen Kimmel, a professor of medicine and epidemiology at the University of Pennsylvania's Perelman School of Medicine. Changing physician and health system workflows, the use of decision support for relaying new complex diagnostic information, the influence of reimbursement, and the development of an evidence base are challenges faced in many health care implementation scenarios. Other areas—such as the return of results to patients and family members and the interpretation of data—are more specific to the field of genomics, observed Kimmel.

Implementation strategies are designed to improve the uptake and sustainability of clinical interventions. Implementation efforts should manage the contingencies of various service systems or sectors, including the challenge of staff training and support, Kimmel said. Rigorously evaluating implementation strategies at early-, mid-, and late-stage endpoints is also important, he added. Failing to understand the barriers and facilitators to a specific intervention can lead to what Kimmel described as a "type III error"—attributing poor outcomes to a failed or ineffective intervention when they were actually a result of poor implementation.

The Implementing Genomics in Practice (IGNITE) Network,[2] is a program funded by the National Human Genome Research Institute (NHGRI), and Kimmel is the principal investigator of the program's coordinating center. The goal of the IGNITE Network is "to enhance and accelerate the use of genomic medicine by incorporating genomic information into clinical care," Kimmel said. The network includes six genomic medicine demonstration projects and a central coordinating center. The subjects of the demonstration projects range from detailed family histories to pharmacogenetics to monogenic diabetes. This is a very forward-thinking and creative approach by NHGRI to study implementation while expanding the knowledge base for genomic medicine, Kimmel said. The network uses the Consolidated Framework for Implementation Research[3] to identify the core implementation components that are common across all of the demonstration projects and to determine which of those factors contribute to successful implementation (Damschroder et al., 2009).

The IGNITE Network research plan includes the identification of common outcomes that define success, the creation of a model for implementation, and the operationalization of constructs through a Likert-type questionnaire that can be adapted for each project. Through the questionnaire, clinicians can weigh in on workflow, knowledge, leadership, beliefs and attitudes, training and self-efficacy, value and utility, group efficacy, and strategies. Example inquiries from IGNITE questionnaires include

- **Workflow:** Staff have enough time to facilitate the integration of [genetic test] into clinical practice
- **Knowledge:** I can find/use reliable sources of the information I need to apply [genetic test] while caring for patients
- **Leadership:** Leaders have openly endorsed and supporting [genetic test] in visible ways
- **Beliefs/Attitudes:** The information generated by [genetic test] is important for patient care
- **Training/Self-Efficacy:** My training has prepared me to treat patients whose family history/genetics place them at high risk for medical conditions

[2]For more information on the IGNITE Network, see http://www.ignite-genomics.org (accessed February 23, 2016).

[3]For more information on the Consolidated Framework for Implementation Research, see http://www.cfirguide.org (accessed February 26, 2016).

- **Value/Utility:** [Genetic test] will improve my ability to care for patients
- **Group Efficacy:** The implementation leaders/team have the necessary qualities and skills to successfully incorporate [genetic test] into my clinical practice
- **Strategies:** A variety of strategies are being used to enable staff to use [genetic test] to assess patient risk

Information from the questionnaires gets collected across a broad range of practice patterns and communities and may help to serve as a sort of "biomarker of implementation," Kimmel said. Such a tool could help indicate what the barriers are and where interventions might be necessary with a particular group of clinicians.

Most of the IGNITE projects do not yet have final results, Kimmel reported, but the network has provided a framework for asking the right questions. IGNITE also has shown that many, but not all, aspects of implementation are generic across projects. For example, one of the IGNITE Network projects is systematically collecting information on all of the barriers to implementation identified across all of the sites, with the barriers being rated by the sites according to how specific they are to genomics. About 25 percent of the barriers to implementation that have been identified are purely genomics-specific, approximately 31 percent are generic, and 43 percent have both genomic and generic components, Kimmel said. Among the genomics-specific challenges are the unknown effects of many novel genetic variants, the incorporation of genetic counseling with the return of results, the integration and formatting of genetic test results in electronic health records (EHRs), the timing and utility of EHR alerts, and reimbursement for testing. Referring to that last issue, Kimmel asked, "How do we do this if nobody is paying for it?" Among the generic challenges are issues with general integration with EHRs, institutional priorities, the underestimation of system-level challenges, provider engagement, and practice workflows. Even with these mixed barriers, the generic components can be rigorously studied to derive results useful for implementation in general. In summary, Kimmel said, genomics implementation has some unique characteristics, but many of its features are common to all implementation programs. The challenges "have to be measured carefully and formally assessed and analyzed so we know what works, what doesn't work, and why."

Both the successful and failed implementations can provide important lessons, Ginsburg said. Publishing such experiences "would be

highly valuable to the community," he added. He also pointed out that the IGNITE Network is producing an implementation toolbox that could provide the community with a sense of what needs to be done. Furthermore, the toolbox is not limited to IGNITE investigators but rather will be open to other networks that are doing implementation of genomics. These other networks should be encouraged to join in and be part of that same toolbox so that information can be shared with all, Ginsburg said.

CELL-FREE DNA SCREENING FOR ANEUPLOIDY

Unbiased clinical effectiveness data is very important for implementing new clinical practices, and translation needs to be evidence-based instead of just rapid, said Mary Norton, a professor of obstetrics, gynecology, and reproductive sciences and the David E. Thorburn, M.D., and Kate McKee Thorburn Endowed Chair in Perinatal Medicine and Genetics at the University of California, San Francisco. The adoption of cell-free DNA screening for aneuploidy was both evidence-based and rapid and therefore makes an excellent case study.

The ability to detect cell-free fetal DNA (cffDNA) in the maternal bloodstream led to the development of non-invasive techniques for fetal aneuploidy screening (Allyse et al., 2013). cffDNA screens were developed from 2000 to 2010 and introduced into medical practice in October 2011 at the same time as the first clinical validation study was published. cffDNA screening is designed to detect fetal genetic abnormalities, such as trisomy 21 (Down syndrome), trisomy 18 (Edwards syndrome), and trisomy 13 (Patau syndrome). In carefully preselected populations, cffDNA screening has extremely high sensitivity, high specificity, and high positive and negative predictive values for Down syndrome, Norton said. Screening for trisomy and other chromosomal abnormalities traditionally has been done using two standard noninvasive tests, an ultrasound in the first trimester and a blood test in the second trimester. A high-risk woman or someone who tested positive to the initial screening undergoes one of two invasive diagnostic tests, chorionic villus sampling or amniocentesis. This conventional approach had a relatively low risk of complications, Norton said—roughly 1 in 1,000 in the most recent analysis, which is not different from the background rate of pregnancy loss. One advantage that cffDNA screening offers is that it has about a 99 percent detection rate for Down syndrome, while the most sensitive version of traditional screening has a detection rate of 92 to 93 percent, Norton said.

There are potential concerns about cffDNA screening, one of which is that while it is excellent at detecting trisomy 21, the test is far less effective at detecting other chromosomal abnormalities such as trisomy 18 or 13. Another concern with cffDNA screening, Norton said, is that it is more expensive than traditional methods. This raises the question of whether adequate counseling is being provided so that patients understand the limitations and benefits of the cffDNA screen. Norton and her colleagues published a comprehensive cost–utility analysis in which they recommended conventional screening methods until women were 40 years old and the risk of Down syndrome was elevated, at which point cffDNA screening became optimal and cost-effective (Kaimal et al., 2015).

The uptake of cffDNA screening has been among the most rapid of any new clinical test, Norton said. By 2014 more than 800,000 cffDNA tests were being performed worldwide (Bianchi, 2015). Evidence in support of cffDNA screening has been compelling, Norton said, although she added that the evidence has come largely from industry-sponsored trials that use carefully selected groups of patients. Another potential reason for the rapid uptake of cffDNA screening is that testing for Down syndrome has been widespread for decades and patients and clinicians are well informed about it. Professional societies have supported Down syndrome screening for many years, though many continue to recommend traditional screening rather than cell-free DNA screening, Norton said. The cffDNA screen was not developed to fill a quality gap; instead, it met a need that people were not asking for in a market that did not previously exist, Norton said. Fetal screening is a very competitive and lucrative industry, she added, which means that commercial laboratories have done considerable marketing.

Several major professional societies have published statements on cffDNA screening for fetal aneuploidy, and the general observation, Norton said, is that conventional screening methods are the most appropriate first line test. Any patient may choose cffDNA screening, according to these statements, but patients should be counseled appropriately regarding the limitations and benefits (ACOG, 2015). In addition, further diagnostic testing is required to confirm abnormal results before irreversible decisions are made.

Norton cited several challenges that have arisen during the rapid uptake of cffDNA screening. Many providers have inadequate knowledge of genetics and statistical factors such as the positive predictive value in low-risk patients, she said. In addition, standardized patient education is

lacking, and many patients think that the cffDNA screen is an alternative to invasive, risky testing, which is incorrect, Norton said. The results of the test also tend to be misunderstood. The lower risk the patient is, the less likely a positive result is to be a true positive, Norton said. For example, a study of 109 consecutive cases of women who had abnormal cffDNA screening results followed by diagnostic testing yielded a true positive or positive predictive value of 67 percent, with the performance higher for Down syndrome than for other less common chromosome abnormalities (Wang et al., 2015). Yet laboratory test results are essentially dichotomized to yes or no, which again can lead to misunderstanding. Poor understanding of the test results could lead some women to terminate normal pregnancies without confirmation.

Norton also called attention to the occurrence of incidental findings that can potentially come along with the cffDNA screening. The cffDNA test sequences both fetal and maternal DNA, so maternal health problems such as malignancies can be detected (Bianchi et al., 2015). Systematic data about incidental findings on mothers are now beginning to be collected, Norton said. The consent forms are usually very standard and indicate only that the patient is having a test for Down syndrome, she said. It is only now being recognized how problematic this can be for patients, she said. Professional societies are considering enacting a credentialing process for test providers along with standardized consent. The lesson that we can learn from cffDNA screening is that rapid implementation can lead to issues down the road, Norton said.

Several large integrated health systems and programs like the California Prenatal Screening Program[4] are working on collecting high-quality evidence about cffDNA screening, Norton said. In addition, the U.S. Food and Drug Administration (FDA) recently called for improving the evidence base for laboratory-developed tests (Office of Public Health Strategy and Analysis, 2015). The FDA report cited cffDNA prenatal testing as one of 20 problematic case studies of laboratory-developed tests that may yield false positive and negative results and, thus, subsequent harm to patients.

cffDNA screening is a "perfect case study for implementation science," said Alexandra Shields of Harvard Medical School and Massachusetts General Hospital. The challenge is to squeeze out the positive clinical benefits of this test and limit the deleterious potential downsides. Enacting a common reporting format for different laboratories would be

[4]For more information regarding the California Prenatal Screening Program, see http://www.cdph.ca.gov/programs/PNS/pages/default.aspx (accessed February 23, 2016).

an important advance, Shields said, as would creating universal patient educational information that is mandated by the FDA. Once women understand what additional information is going to be generated by that test, they could communicate what they would like back in the returned results, and this information could be flagged in the EHR. If a patient does not want certain types of information, the EHR could help minimize errors in disclosing information.

PROVIDING GUIDANCE FOR IMPLEMENTATION

Most innovations are not self-implementing, and those that are often are implemented inappropriately, Mittman said. For example, clinical practice guidelines would ideally be issued with accompanying implementation guidance. In an ideal world, the groups developing new practices would take on the responsibility of providing the supporting implementation guidance, the necessary tools, and patient and clinician education materials. This would require convening all of the stakeholders, including regulators, policy and practice leaders, fiscal intermediaries, payers, clinical leaders in the systems, and so on. Companies that produce genomic tests could get together with clinicians to develop standardized formats for delivering test results. "It's another example of the principle of engagement, partnership, and collaboration," Mittman said. Requirements from the FDA, the medical community, and professional societies may ensure that new innovations are accompanied by guidance and supporting tools, he said.

5

Genomics and Implementation at the Level of Population Health

Important Points Highlighted by Individual Speakers

- Genomic information can be leveraged to improve the health of broad populations through the implementation of statewide policies that increase the use of genetic risk assessment techniques for common chronic conditions such as cancer. (Duquette)
- Educating leaders of health insurance plans about genomics-based approaches for disease prevention and treatment can help promote consistent genetic testing and counseling policies. (Duquette)
- Implementing genomic testing for maturity-onset diabetes of the young in high-risk populations could lead to the diagnosis and effective treatment of patients who may otherwise be misdiagnosed as having type 1 or type 2 diabetes. (Pollin)
- Using whole-exome sequencing to improve the diagnosis rate of pediatric genetic disorders could provide experience and momentum that can be applied to the design of future programs targeting more prevalent diseases such as cancer or heart disease. (LePage)
- Engaging more clinicians in genomic research projects would accelerate the uptake and translation of new genomic applications by patients and providers in clinical care settings. (LePage)
- The methods and tools of implementation science can be used to help create a common framework for incorporating genomics into clinical practice by drawing from other disciplines such as management sciences, organizational design, and engineering. (Mittman)

As novel genomic approaches move into routine practice, health care systems are routinely encountering new challenges. Examples of the impediments faced by health care systems in these situations are limited clinician knowledge about genomics, inconsistent reimbursement policies, and the need to analyze a complex evidence base to justify the new procedure. This chapter describes the challenges and successes encountered by three programs that are currently integrating genomic approaches to human disease prevention, diagnosis, and treatment (see Box 5-1). The programs described in this chapter, which are all at different points along the translational pipeline, include a statewide cancer genomics program, a coordinated effort to provide genomic diagnoses to people with monogenic diabetes, and a small pilot program that explored the genetic basis for rare childhood diseases.

BOX 5-1
Potential Factors Affecting Genetic Test Implementation

Possible barriers to implementation proposed by individual speakers

- Lack of awareness about gene-disease associations for diagnosis (Pollin)
- High costs associated with running a genetic test/panel (Pollin)
- Incomplete evidence base supporting clinical use of a specific gene or test (Pollin)
- Uncertainty around reimbursement policies (Duquette, Pollin)
- Limited guidance from professional societies (Pollin)
- Limited funding for pilot genomics projects (LePage)

Possible facilitators of implementation (proposed by Duquette)

- Engaging stakeholders early, during the needs assessment phase
- Ensuring adequate staffing by bringing on experts
- Enlisting multidisciplinary partner organizations to support implementation

A STATEWIDE CANCER GENOMICS PROGRAM

In 2002 the Health Resources and Services Administration provided funding to a small group of states, including Michigan, to perform stakeholder needs assessments and develop statewide genetics plans. As part of its needs assessment, the Michigan Department of Health and Human Services (MDHHS) engaged hundreds of stakeholders, including patients, clinicians, researchers, teachers, and other representatives to determine what was desired from a state health department in terms of genetics. One message that came through quite clearly, according to Debra Duquette, genomics coordinator at the MDHHS, was that stakeholders wanted a more comprehensive genetics program that went beyond newborn screening and examined prevalent chronic diseases such as cancer, diabetes, and cardiovascular disease. At the same time, Michigan's cancer division received many questions about hereditary breast and ovarian cancer, which led to the realization that expertise was needed on staff to address issues regarding genomic medicine on a population health level. As a result, a full-time genomics coordinator and a part-time cancer genetics coordinator were brought on, Duquette said.

The Michigan Cancer Genomics and State Genetics Plan that emerged from this process had six discrete goals designed to improve traditional maternal and child public health genetic services as well as to create a more comprehensive agenda covering common chronic diseases with onset in adult life (see Box 5-2; Michigan Department of Community Health, 2004).

In 2003 Michigan entered into a 5-year cooperative agreement with the Office of Public Health Genomics in the Centers for Disease Control and Prevention (CDC) in an effort to integrate genomics into the chronic disease realm. In 2008 Michigan received additional funding from the CDC to implement and disseminate information about genetic tests with a strong evidence base such as those used for BRCA1 and BRCA2 screening and tests for Lynch syndrome.

BOX 5-2
Goals of the Michigan Cancer Genomics and State Genetics Plan (as presented by Duquette)

- Increase genetic literacy in the state of Michigan.
- Assess the public health impact of heritable conditions and the utilization of genetic services.
- Improve access to genetic information, prevention strategies, and services.
- Promote the early identification and treatment of individuals with birth defects, heritable disorders, or genetic susceptibilities throughout the life cycle.
- Identify best practices and promote a policy framework to assure high-quality services, supports, and genetic privacy protections.
- Promote appropriate public health responses to advances in genomics medicine and technology.

In 2014 the state entered into its fifth cooperative agreement with the CDC's Division of Cancer Prevention and Control. As part of this most recent project, Michigan is implementing education and surveillance systems for Lynch syndrome and for hereditary breast and ovarian cancer. According to Duquette, this effort aligns with Healthy People, an initiative of the Office of Disease Prevention and Health Promotion. Healthy People proposes 10-year national objectives designed to improve the health of Americans, and two of the objectives in the most recent Healthy People 2020[1] plan involve the use of genomics-based tools for improving the health of the overall population. The two genomics-specific goals of Healthy People 2020 are:

- To increase the proportion of women with a family history of breast and/or ovarian cancer who receive genetic counseling.
- To increase the proportion of persons with newly diagnosed colorectal cancer who receive genetic testing to identify Lynch syndrome (or familial colorectal cancer syndromes).

[1]For more information regarding Healthy People 2020, see http://www.healthypeople.gov (accessed February 26, 2016).

The Comprehensive Cancer Control Plan for Michigan for 2009–2015 included a plan to increase the availability of cancer-related genetic information to the Michigan public and decrease barriers to risk-appropriate services. To achieve these aims, the Cancer Control Plan included three implementation objectives (Michigan Cancer Consortium, 2014):

- By 2011, expand public knowledge about the impact of genetics on cancer risk and management (breast, ovarian, and colorectal cancers).
- By 2015, expand provider knowledge about the impact of genetics (breast, ovarian, and colorectal cancers) on cancer control.
- By 2015, improve genetic health care financing and access to testing and support services.

Implementing the Program

To support the implementation of these objectives, a multidisciplinary group of partners was enlisted, including federal organizations, state and local agencies, clinical practices, providers, patients, and families. One partner organization, the Michigan Cancer Consortium, is a network that includes more than 100 public and private groups working toward cancer prevention and control. The state's cancer control plan also helped facilitate the creation of the Michigan Cancer Genetics Alliance network, which currently has about 250 members and has been an important part of the effort, Duquette said.

There are 25 health plans in place in Michigan that cover the vast majority of its 10 million residents, Duquette said. State officials have been working to educate health plan leaders on the best practices for hereditary breast and ovarian cancer. A major partner in this effort is the Michigan Association of Health Plans, a group that disseminates information to its constituents about cancer genomics policies, among other issues, in the form of a quarterly newsletter.[2]

The MDHHS developed specific metrics to assess genetic counseling, testing, and management policies pertaining to BRCA1 and BRCA2. When a health plan performs well on every metric, it receives an honor from the department, Duquette said. The number of plans qualifying for

[2]To view newsletters from the Michigan Association of Health Plans, see http://www.mahp.org/resources/insight-newsletter (accessed February 24, 2016).

awards has steadily increased, from 4 when the work began to 16, covering more than 80 percent of the population, she said. Data are collected from every board-certified or board-eligible genetic counselor in the state who is involved in BRCA counseling. Currently, the database includes information on more than 17,000 patients and is useful for addressing open questions such as how insurance coverage affects testing.

Much work has been done to reduce barriers for people who were not able to receive BRCA testing because of inadequate insurance coverage, Duquette added. In 2008, approximately 22 percent of the population receiving genetic counseling were not able to get BRCA testing because of inadequate insurance coverage, she said, but by 2014 that percentage had decreased to just over 8 percent.

There are vast differences in coverage policies for BRCA testing and counseling among private and public payers (Wang et al., 2011). Many of the health plans in Michigan previously covered counseling and testing solely for BRCA1 and BRCA2; however, several payers have moved away from gene-specific coverage to indication-specific policies, Duquette said. Indication-specific testing refers to genetic screening performed in response to specific clinical indications that fall into categories such as pediatric, preconceptional/prenatal, and adult-onset conditions (Pletcher et al., 2007). However, implementers, such as state health departments, could benefit from returning to the original system where reimbursement policies on genetic testing and counseling were categorized in a gene-specific manner, Duquette said.

IDENTIFYING DIABETES SUBTYPES: A MODEL FOR GENOMIC MEDICINE

A bottom-up approach to genomic medicine has taken place in the field of diabetes research, said Toni Pollin, associate professor in the Department of Medicine and the Department of Epidemiology and Public Health at the University of Maryland School of Medicine. In 2006 a genetic test was conducted on a sample from a young girl who had been diagnosed with type 1 diabetes at 1 month of age and was reliant on an insulin pump. The test results surprisingly indicated that she did not have type 1 diabetes, but instead possessed a rare mutation in a potassium channel subunit that was the cause of her illness. After she started a new treatment regime at the Clinical Research Center of the University of

Chicago, her islet cells started to produce their own insulin within a few weeks, and she became completely free of her insulin pump, Pollin said.

Type 1 and type 2 diabetes, the most common forms of the illness, are polygenic, meaning that multiple genes contribute to the risk of developing the disease (National Diabetes Information Clearinghouse, 2007). The young girl described by Pollin did not have type 1 or type 2 diabetes, but instead had an illness that is classified as monogenic diabetes. Monogenic diabetes encompasses rare forms of the illness that are caused by a mutation in a single gene, and they can be overcome in certain cases with high doses of sulfonylureas, drugs used to stimulate the release of insulin from the pancreas. The two forms of monogenic diabetes—neonatal diabetes mellitus and maturity-onset diabetes of the young (MODY)—account for 1 to 5 percent of all diabetes cases in young people (National Diabetes Information Clearinghouse, 2007).

MODY is often misdiagnosed as either type 1 or type 2 diabetes, Pollin said, but such misdiagnosis can be avoided with genetic testing. The majority of MODY cases are caused by defects in genes that code for transcription factors active in pancreatic beta cells or by defects in glucokinase, which is required for the phosphorylation of glucose to glucose-6-phosphate, she said. Once the disease is properly diagnosed, many MODY patients can transition from insulin to sulfonylureas without loss of glucose control (Shepherd et al., 2009). The proper diagnosis and transition away from insulin is important for patients and their families, Pollin said, because it eases the therapeutic burden and improves quality of life.

The SEARCH for Diabetes in Youth study, a multicenter examination of the etiology of diabetes in young people, found that monogenic diabetes is underdiagnosed (Pihoker et al., 2013). Although only a small percentage of patients have monogenic diabetes, this group still represents hundreds of thousands of people in the United States, Pollin said. Furthermore, MODY mutations occur across all minority groups, so populations at high risk for childhood obesity, including Hispanics and African Americans, may be particularly underdiagnosed, Pollin said.

MODY presents a compelling opportunity to implement genomic medicine, Pollin said, but the field faces a lack of awareness—many people have never heard of these forms of diabetes, and clinical overlap can lead to trouble differentiating between the types. Some algorithms for diagnosis are available, but no perfect approach exists, Pollin remarked. Additional challenges include the high cost and complexity of the current tests, intellectual property concerns, and limited professional

society guidance, she said. Finally, patients and physicians alike are largely unaware of how much a proper diagnosis can change a patient's life. For all these reasons, Pollin said, it is important to assemble a strong evidence base that demonstrates why diagnosing MODY is beneficial.

Improving the Evidence Base

The Personalized Diabetes Medicine Program at the University of Maryland, a component of the IGNITE project, is aimed at strengthening the evidence base on genomic approaches for detecting MODY. Researchers are trying to identify patients who may have monogenic diabetes. Pollin described their approach, which begins with a patient questionnaire that clarifies several aspects of family history and initial diagnosis. The results of the questionnaire are used to determine if further clinical workup or sequencing is needed. If a patient is referred for sequencing, he or she is tested for a panel of 40 known monogenic diabetes genes. In those patients where sequencing reveals a pathogenic variant, test results are added to the electronic health record (EHR), and customized treatment begins, with genetic counseling and testing for family members. If a variant of unknown significance is found, further family and functional studies are performed. Finally, the impacts are evaluated through patient- and provider-reported outcomes.

The program is interested in disseminating its findings, especially to genetic counselors and clinical geneticists, in order to facilitate accurate diagnoses as early as possible. In order to efficiently translate their research findings to clinical care, the Personalized Diabetes Medicine Program staff members are liaising with hospital administrators at the University of Maryland, Pollin said.

Covering the Test Panel

A payer advisory panel working with the Personalized Diabetes Medicine Program indicated that payers are primarily interested in covering those genetic tests with demonstrated clinical utility, Pollin said. An interesting conundrum has taken place with payers over the number of genes on the monogenic diabetes panel, Pollin said. Payers often will only want to cover the subset of genes on a panel for which the clinical utility has already been clearly demonstrated. For example, if 5 of 40 genes have strong evidence to support clinical use, payers do not want to cover the costs of testing the other 35 genes, she said. In response to the

objection that the full panel costs no more than a partial panel, the payers have indicated that they do not want to see the results of the other 35. It is important to consider that the additional genes on the panel may strengthen the evidence base and lead to improved testing and interventions, Pollin said.

GENOMICS PILOT PROJECTS IN CANADA

Génome Québec recently launched the Integrated Clinical Genomic Centre in Pediatrics in collaboration with Centre Hospitalier Universitaire Sainte-Justine, said Marc LePage, president and chief operating officer of Génome Québec. The pediatric genomics center is the first of its kind in Canada and is attempting to overcome diagnostic challenges in children with rare genetic diseases. Pediatric genetic disorders affect approximately 500,000 children in Canada, and many of the genes that cause these disorders are unknown because gene-discovery studies are especially challenging with limited patient samples. Of those 500,000 affected children, 50 percent do not receive a diagnosis and 40 percent receive an incorrect diagnosis, LePage said.

In an effort to improve the diagnosis of rare genetic diseases, the pediatric genomics center developed a pilot project in which the center provided the sequencing capacity to examine a small cohort of children with undiagnosed illnesses, LePage said. Researchers carried out exome sequencing in 96 children, which resulted in a molecular diagnosis for 37 percent and a tentative diagnosis that required further confirmation for an additional 15 percent. This represents a major step forward because a diagnosis often means better clinical care for these patients, LePage said.

Now that the pilot project is finished, LePage and his colleagues are envisioning much larger studies that would tackle genomics issues in cardiology, oncology, neurology, and other fields, with Génome Québec providing the centralized sequencing and clinical accreditation. The pilot research project on rare diseases gave Génome Québec the initial momentum and small-scale experience needed to take on a bigger challenge, LePage said.

The biggest issue facing Génome Québec during the pilot projects, he said, is the funding gap that exists between research and the health care system. Research agencies are hesitant to fund projects that are in the clinic, and vice versa, LePage said. It is important to make further

inroads into the clinical arena, he said, to bring the results of research to patients and providers. "That is our challenge in this field right now."

A National Bioresource Network

In addition to its support of pilot projects in genomics, Génome Québec is working to expand national bioresources. In 2007 a databank known as CARTaGENE was created to collect and store biological material specific to Québec (see Chapter 3). The CARTaGENE bioresource is now one of five regional projects that are part of the Canadian Partnership for Tomorrow Project (CPTP), a pan-Canadian network that stores clinical information and biological samples from approximately 300,000 people (Borugian et al., 2010). CARTaGENE was initially designed as an ongoing prospective investigation of the environmental, lifestyle, and genetic influences on cancer, but its reach is spreading to other chronic diseases now, LePage said. The CARTaGENE cohort consists of male and female participants ranging in age from 40 to 69, which is the demographic at the highest risk for developing chronic disorders (Awadalla et al., 2013). Participants will be followed on a long-term basis in order to better understand the influence of genetics and environment on health and disease.

AN INTERDISCIPLINARY FRAMEWORK FOR TEST IMPLEMENTATION

The principles of implementation science can be used to help build a common framework for incorporating genomics into clinical practice by drawing from other disciplines such as the management sciences, organizational design, and engineering, said Brian Mittman of Kaiser Permanente Research. In some cases, patient care will be customized and unique; in other cases, it will be routine. If a generic framework similar to a standard operating procedure existed, the appropriate customizations and individualization could be applied as needed, Mittman said.

Given the inertia of clinical care, leaders of health care systems must make challenging decisions between wholesale change and implementing single applications. Alexandra Shields of Harvard Medical School and Massachusetts General Hospital supported the idea of thinking about one application at a time. Shields cautioned against placing genome-wide sequencing results directly into patients' EHRs with the idea that they

will become useful someday because that approach does not have the infrastructure or resources to support it. However, she also noted that infrastructure and resources could be standardized moving forward, so that the investigation of genomic applications becomes routinized. This process could encompass patient education, ethical issues associated with consents and the return of results, and follow-up genetic counseling. Such supports could "realize the benefits of genomic medicine that apply to all different cases," Shields said.

Developing completely unique methods for implementing every genomic application is a challenge, said Robert McDonough of Aetna. He emphasized the value of a common framework for evaluating genomic tests and their implementation. From a payer's perspective, he observed, an overarching framework to deal with the plethora of tests would make it easier to consider the unique aspects of an individual test. A process similar to this is occurring in oncology, said Jane Perlmutter of the Gemini Group, where the mentality is shifting away from thinking of cancer by organ site and more toward classifying cancer by the genetic mutations.

6

Achieving the Vision

Over the course of the workshop, several themes emerged which highlighted areas in genomic medicine that may benefit from the tools and approaches of implementation science. Genetic research has contributed a great deal to the understanding and treatment of human diseases, and the adoption of genomic medicine holds tremendous potential to improve public health (Green et al., 2015). However, evidence suggests that individuals from minority populations and disadvantaged socioeconomic backgrounds receive fewer therapeutic interventions and poorer quality medical care (AHRQ, 2015). Several workshop speakers pointed out that in order to ensure equitable access to genomic medicine, greater efforts will be required to address health inequities across low income and minority groups.[1] To maximize the benefits of genomic medicine across populations, patients and study participants will need adequate knowledge about genomics that allows them to make well-informed health decisions (Hurle et al., 2013). Projects aimed at increasing genomic literacy among patients, providers, and the public would facilitate a more efficient uptake of genomics into clinical practice, said Bernice Coleman of Cedars Sinai Medical Center, Los Angeles. Finally, additional research and recommendations that address the variability in reimbursement policies for genomic applications may help to accelerate their uptake, said Robert McDonough of Aetna.

In the final session of the workshop, a panel of stakeholders individually proposed actionable next steps that could potentially improve and accelerate the translational pipeline for genomics. Box 6-1 contains suggested next steps from the individual workshop speakers.

[1]For more information and background reading on potential health disparities and building trust, see Appendix F.

BOX 6-1
Possible Next Steps Proposed by Individual Speakers

Individual ideas about how implementation science may be applied to genomics to address issues in health disparities, literacy, and coverage and reimbursement:

- Encourage patient-centered outcomes research as a way of engaging patients, families, and other key stakeholders, to increase transparency, provide higher-quality care, and enhance trust in genomic medicine practices. (Chambers, Perlmutter, Wilkins)
- Design a program for physicians where the goal is to build confidence and skill in delivering genomic medicine across all populations. One aspect of the program could focus on refining the way in which results from genomic tests are interpreted and communicated to patients. (Chambers, Shields)
- Engage leaders across health care systems in a discussion about how the tools and approaches of implementation science can be part of a cultural change to make the introduction of genomics into the clinic more efficient. (Coleman, Faucett, Ginsburg, Mittman)
- Increase public awareness about the potential benefits and limitations of genomic approaches with educational and engagement programs that focus on preventing, diagnosing, and treating human diseases. (Chambers, Coleman, Wilkins)
- Collect information on case studies of exceptional integration of genomic medicine along with failed attempts, in an effort to identify outcome metrics and the qualities of highly successful implementation. (Chambers, Norton, Shields)
- Develop a common framework for payers and policy makers to evaluate the validity of rapidly evolving genomic tests. (McDonough)
- Obtain guidance from leading medical and scientific professional organizations on the best practices associated with genomic applications related to their field, as a way of promoting consistent reimbursement policies among payers. (McDonough, Norton)
- In developing coverage and reimbursement policies, consider the whole clinical service from ordering a genetic test to the follow-up care related to that test. (Shields)

ADDRESSING HEALTH DISPARITIES IN GENOMIC MEDICINE

Because genome-wide association study (GWAS) data often come from populations that lack diversity, the genetic applications developed from those data may be useful only for certain groups (Haga, 2010). Even when the evidence base for genetic applications represents a diverse population, there is a need to ensure that the benefits of those data are equitably distributed across the population (see Figure 6-1), said Alexandra Shields of Harvard Medical School and Massachusetts General Hospital. At each stage in genomic research and the clinical uptake of that information, there is the possibility that a health disparity can be introduced, which is why Shields reminded the audience that "genomics will only achieve its full potential to improve health when the advances it engenders become accessible to all" (Green and Guyer, 2011).

One important contribution that could be made toward addressing health disparities, Shields said, would be to research and share information on a case study that successfully applied implementation science to avoid such disparities. A case study in genomics could report on a number of implementation issues, including

- Knowledge and evidence gaps
- Provider readiness
- Patient willingness
- Coverage and financing
- Data infrastructure, including health information technology
- New or expanded roles for personnel in implementation and the associated costs
- Outcomes and emerging evidence

Some of the same issues were described as possible barriers to and facilitators of implementation by individual speakers in Chapter 5 (see Box 5-1).

To prioritize which health conditions to use as a potential case study, Shields suggested considering the prevalence, cost, mortality, and health disparities of different diseases. As an example, she noted that cancer introduces health disparities among racial groups and is highly prevalent, extremely costly, and carries high rates of mortality. Furthermore, oncology is an area that adopted genomics early and thus may offer opportunities to learn about the challenges and successes of implementation. In developing a

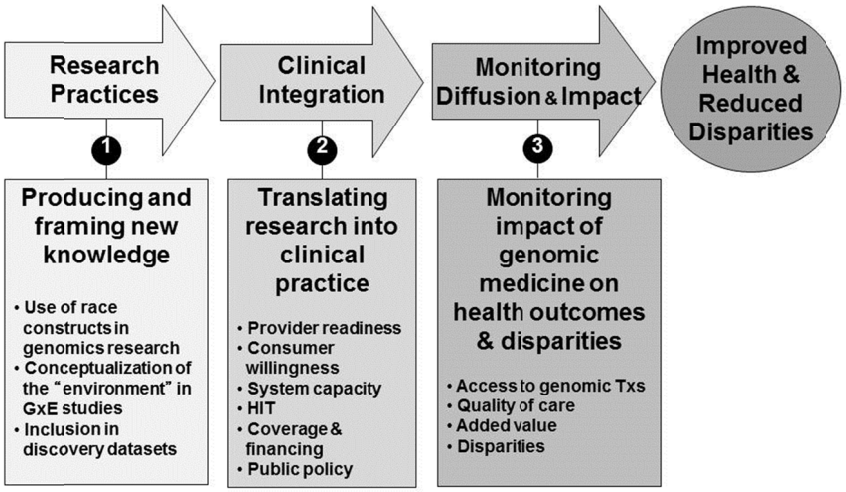

FIGURE 6-1 The translational pipeline from genomics research to the clinic, indicating possible areas where health disparities can be introduced.
NOTE: GxE = gene–environment interaction; HIT = health information technology; Txs = therapies.
SOURCE: Alexandra Shields, National Academies of Sciences, Engineering, and Medicine workshop presentation, November 19, 2015. Figure was developed in discussions with Harvard/Massachusetts General Hospital Center on Genomics, Vulnerable Populations, and Health Disparities. For more information on the Harvard/Massachusetts General Hospital Center on Genomics, Vulnerable Populations, and Health Disparities, see http://cgvh. harvard.edu (accessed February 26, 2016).

case study, it is important to examine the evidence base carefully, Shields said. For example, for oncology genomics research, Lynch syndrome and BRCA-associated hereditary breast and ovarian cancer might have the strongest overall evidence bases, but, she asked, are there data available across all populations? Whether the somatic mutations discovered to date largely in white populations are present in minority patients at the same rate is an unanswered question that needs to be addressed, Shields said.

Provider readiness is another issue that arises when addressing health disparities in genomic medicine. Providers who care for poor and minority communities might believe that genomic medicine is too esoteric, given the health needs of the populations they serve, Shields said. In a national survey of 2,000 primary care physicians, only 5 percent said they felt very confident in their ability to interpret genetic tests, and only

4 percent felt prepared to counsel patients considering genetic testing (Shields et al., 2008).

According to that survey, physicians serving minority populations or a disproportionate number of Medicaid patients were less likely to order genetic tests for their patients than physicians who saw fewer minority patients or those with Medicaid, Shields said. In short, genomic applications are not reaching minority and low-income patients at the same rates as other populations, she said.

Different communities can have highly variable cultural beliefs and preferences which may be important to take into account when designing implementation projects. The opportunity for implementation science to affect how genomics is incorporated into practice lies at the intersection of understanding a high-priority condition and persistent health disparities, Shields said.

IMPROVING LITERACY IN GENOMICS AND IMPLEMENTATION SCIENCE[2]

Implementation science could potentially be useful for educating members of all population groups and recruiting them to participate in studies, said Bernice Coleman of Cedars Sinai Medical Center, Los Angeles. The need for greater literacy in genomics and implementation science among all stakeholders was a topic addressed by individual speakers including Coleman, Jane Perlmutter of the Gemini Group, Consuelo Wilkins of the Meharry-Vanderbilt Alliance and Vanderbilt University Medical Center, and David Chambers of the National Cancer Institute.

Efforts to enhance genomic literacy would benefit the public and potentially prevent future misunderstandings about genomic medicine, Perlmutter said. Early in 2015, President Obama announced the Precision Medicine Initiative (PMI), a plan aimed at improving disease treatment and prevention by accounting for individual variability in genetics and environment. While the announcement generated a great deal of public

[2]On March 2, 2016, the Roundtable on Health Literacy of the National Academies of Sciences, Engineering, and Medicine conducted a workshop titled Health Literacy and Precision Medicine: An Important Partnership. To read more about the workshop and the issues that surround the role of health literacy in the growing field of precision medicine, see: http://www.nationalacademies.org/hmd/Activities/PublicHealth/HealthLiteracy/2016-MAR-2.aspx (accessed April 13, 2016).

enthusiasm, many came away with a misunderstanding about how long it is likely to take for most people to personally benefit from precision medicine, Perlmutter said. Although some areas, such as newborn screening and oncology, are further along than other fields in the implementation of genomics, she said, generally speaking, additional research will be needed for the PMI to reach its full potential even in these areas. It will be very important to be upfront with the public about the current benefits and limitations of genomic medicine, Perlmutter cautioned. Genomic information is different from other health care data in that some of it is not currently clinically actionable, Shields observed. However, what is not currently actionable may become important in the future. Health care systems have an obligation to ensure that patients have a complete understanding of what information is generated by a test, Shields said, so that they can make an informed decision about how to manage test results. Patients should be able to decide if they want genomic information stored in their electronic health record (EHR) and how they want to proceed with disclosure of results to themselves or family members.

Perlmutter also noted that there is often confusion about the differences between research and practice. For example, when researchers say a discovery will be in the clinic within 2 years, they often mean in phase I clinical trials, whereas a patient might interpret that as meaning that the discovery will be available from a doctor in 2 years, she said.

Involving Stakeholders Early in the Process

As demonstrated by some of the cases discussed at the workshop, involving patients and advocates from the very beginning can help strengthen genomic literacy, Perlmutter said. In certain instances, clinical study endpoints are not as important as they could be because it is not really known what patients want and need, Perlmutter said. For example, privacy, security, and family issues are major concerns for some patients, she said, and "we need to talk about these issues." However, involving people early generates buy-in, she observed. While efforts to disseminate information to clinicians are laudable, unless there is a parallel effort to help the public understand and embrace genomics, problems will arise, Perlmutter added.

Implementation science could help set standards for educating minority or low-income patients on these issues, which would require adequate genetic counseling, Shields said. Enrollment in biobanks often occurs through an opt-out rather than an opt-in policy, which can result

in confusion for patients. Ensuring that adequate information is provided to patients before they submit samples to biobanks will help prevent distrust over the use of the samples.

Engaging Health Care System Leaders About Genomics

Implementation science has the potential to be a key facilitator in the movement of genomics into practice, and it may provide insights on both top-down and bottom-up approaches, Coleman said. The leaders at hospital health care systems need to be on board for change to occur, as was the case with the Geisinger Health System, said Geoffrey Ginsburg, the Roundtable's co-chair and the director at the Duke Center for Applied Genomics & Precision Medicine (see Chapter 3). Health care system leadership plays a key role in changing cultures, setting frameworks, and providing incentives, feedback, and motivation. Therefore, Coleman said, it is important to increase literacy on genomics and implementation science among health care system leaders so that novel approaches can be integrated efficiently. It may be beneficial for implementation scientists and researchers to work hand in hand to design research projects that evaluate current practices, identify gaps, and benefit all populations. One key component to successfully monitoring outcomes, Coleman added, is to identify evaluation metrics in advance through collaboration with stakeholders.

COVERAGE AND REIMBURSEMENT CONSIDERATIONS

Reimbursement is necessary but not sufficient for the successful implementation of genomic approaches in medicine, Aetna's Robert McDonough emphasized. A nascent field known as reimbursement science is aimed at standardizing the way that payers, guideline developers, and health care policy makers create reimbursement parameters, McDonough said. One of the goals of reimbursement science is to create tools and approaches for assessing the effectiveness and value of products that are covered by public and private health plans. Findings from reimbursement science could hasten the delivery of useful products and therapies to patients in need.

Genomic testing presents special challenges to reimbursement science because of the rapid evolution of new technologies, McDonough said. The Center for Medical Technology Policy and the Tapestry Net-

work and its Sustainable Predictive Oncology Therapeutics and Diagnostics (SPOT/Dx) program have developed guidance for payers and other policy makers on evaluating the validity of genomic tests. Most of the work thus far has focused on oncology; however, it is applicable to other types of genomic tests. If product developers in genomics had a clear understanding of the requirements for inclusion in coverage policies, it would be easier to predict whether their tests would receive reimbursement, McDonough said.

Genomics often focuses on rare conditions; therefore, payers are more likely to rely on guidelines, rather than an incomplete evidence base. One example of a genomic test with a very solid evidence base was cell-free fetal DNA (cffDNA) testing for aneuploidy, McDonough said (see Chapter 4). The cffDNA test received recommendations from major professional societies, leading to consistent reimbursement among payers and rapid adoption into clinical practice. In contrast, testing for maturity-onset diabetes of the young (MODY) poses more challenges, McDonough said (see Chapter 5). The criteria for whether or not to perform screening are inconsistent, and the condition is relatively rare. Consistent guidance from the leading professional organizations on when MODY testing would be appropriate would help enable consistent coverage policies, McDonough said. Payers are not just passive participants; instead, they can be important for promoting valuable tests to their constituents. Most payers now have programs in which they use their own data to identify care gaps and alert physicians and patients to those gaps, he said.

Payers are considering options such as bundled payments or risk-sharing agreements so that genetic tests are accompanied by treatment and an entire continuum of care, McDonough said. If the genetic test was included in the bundle for a condition, the payer would not have to assess individual claims for a test; however, it is not known whether that would increase or decrease the uptake of the test or how it would affect implementation.

Coverage for genomic panels has been a complicated issue. McDonough pointed out that no consensus exists as to what should be covered on any given panel. Furthermore, though the costs of testing have been going down, the cost to payers has been going up, McDonough said. Higher costs are part of the reason why payers are reluctant to allow additional components of the test to be covered, he said, and even though the additional incremental cost to the lab is negligible, that does not necessarily correspond to how the insurer is billed.

An effort to research and showcase model reimbursement policies that would apply to many of the key stakeholder groups, including payers, would help advance the field, said Brian Mittman of Kaiser Permanente Research. This would set an important precedent in this era of considerable ambiguity, uncertainty, and heterogeneity in genomic medicine policies, he said.

IMPLEMENTATION SCIENCE AND GENOMICS: THE ROAD AHEAD

A tremendous opportunity exists for integrating implementation science into genomics, Chambers said. At the end of the workshop, he summarized several of the main points of the presentations, and he highlighted possible approaches for using implementation science-based approaches to advance genomics. First, for ongoing and future discovery studies he suggested that researchers try to capture and quantify how clinicians, patients, and health systems are using the findings. Hybrid studies that examine effectiveness alongside implementation measures may be useful for reducing the amount of time it takes to integrate a research discovery in the clinic (see Chapter 2). Gaining an understanding of the demand for genomic tests and working toward enhancing that demand by increasing genomic literacy across all population subgroups is critical, Chambers said.

Secondly, within existing implementation science efforts, stakeholders can gather useful knowledge from case studies of "exceptional implementation," instances of rapid uptake of genomic applications, as well as of failures—or "unsuccesses," as Chambers called them. Assessing the qualities of highly nimble and adaptive implementation processes will be useful for future efforts, Chambers said. Clarifying the short- and long-term outcomes of success, along with designing a set of common report forms for patients and families, could help to streamline the process.

Finally, leveraging existing health systems and networks, such as those at the state level, may be useful during implementation, as was shown by Debra Duquette, genomics coordinator at the Michigan Department of Health and Human Services, in her explanation of the work of that department (see Chapter 5). Improving the interpretation of and communication about existing tests will enhance the trust between patients and the health care system, Chambers said. Overall, a patient-centered approach could help integrate testing and research within clinical

practice. Such an approach may require better strategies, increased transparency and disclosure, more inclusiveness, higher quality care, increased use of metrics, and even the minimization of travel inconveniences.

Overall, Chambers said, implementation science seeks to create generalizable knowledge that can be applied to a variety of challenges over a spectrum of disciplines. Even where a specific finding does not have a natural link to a different test or field, lessons can be derived that have a broader impact. "Sometimes we get lost in tests," Chambers said, but "the reality is that there are a lot of people who we are trying to help." We need to think of the young girl, for example, still searching for a diagnosis with her family, "who has interfaced with the health care financing system and has found that there are still tests that are not currently insured. . . . How do we navigate, how do we implement effectively, this entire cascade that would yield the best possible outcomes for her" and for all patients that are in need of finding answers?

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A

Workshop Agenda

Applying an Implementation Science Approach to Genomic Medicine: A Workshop
November 19, 2015

National Academy of Sciences Building
Lecture Room
2101 Constitution Avenue, NW
Washington, DC

MEETING OBJECTIVES

- To elucidate options for accelerating the pace of implementation and evidence generation in genomic medicine by convening medical implementation science experts with stakeholders representing the continuum of genomics translational research.
- To discuss possible strategies for reaching and engaging diverse populations when introducing genomic medicine into practice.
- To explore the challenges, successes, and best practices that facilitate rapid and appropriate translation of genomic knowledge from early discovery to population health.

AGENDA

8:30–8:35 a.m. **Welcoming Remarks**

Sharon F. Terry, *Roundtable Co-Chair*
President and Chief Executive Officer
Genetic Alliance

Geoffrey Ginsburg, *Roundtable Co-Chair*
Director, Duke Center for Applied Genomics & Precision Medicine; Professor of Medicine and of Pathology and Biomedical Engineering, Duke University Medical Center

INTRODUCTION: OPPORTUNITIES IN GENOMICS THAT CHALLENGE THE TRADITIONAL IMPLEMENTATION PATHWAY

Objectives: To define and explore the stages and roles of implementation science from basic science discoveries to advancing genomic medicine in routine clinical care

8:35 a.m. **Charge to Workshop Speakers and Participants: Considering the Role of Implementation Science Across the Translational Spectrum in Genomics**

Greg Feero, *Workshop Co-Chair*
Associate Editor, *Journal of the American Medical Association*; Faculty, Maine Dartmouth Family Medicine Residency Program

Debra Leonard, *Workshop Co-Chair*
Professor and Chair of Pathology and Laboratory Medicine
University of Vermont Medical Center

8:45 a.m. **Overview of Implementation Science: Methods and Approaches**

David Chambers
Deputy Director for Implementation Science
National Cancer Institute

Brian Mittman
Research Scientist III, Research & Evaluation
Kaiser Permanente Research
Senior Advisor, Veterans Affairs Center for Implementation Practice and Research Support, Los Angeles, CA
Consultant, University of California, Los Angeles, Institute for Innovation in Health
Senior Advisor, RAND Health

9:30 a.m. **Clarifying Questions**

SESSION I: DESIGNING FOR IMPLEMENTATION: ENGAGING LARGE POPULATIONS FOR ANALYSIS

Objectives: To assess best practices for engaging diverse patient and provider groups and evaluating how information collected from large groups could be leveraged for discovery efforts and improved health outcomes

Moderator: Bruce Blumberg, Institutional Director of Graduate Medical Education, Northern California Kaiser Permanente

9:40 a.m. Andrew Faucett
Director of Policy and Education
Geisinger Health System

Consuelo H. Wilkins
Executive Director, Meharry-Vanderbilt Alliance
Associate Professor of Medicine
Vanderbilt-Ingram Cancer Center

Marc LePage
President and Chief Executive Officer
Génome Québec

10:30 a.m. **Break**

10:45 a.m. **Discussion with Speakers, Reactants, and Attendees**

Speakers

Andrew Faucett
Consuelo H. Wilkins
Marc LePage

Reactants

Bernice Coleman
Nurse Scientist and Nurse Practitioner
Heart Transplantation and Mechanical Assist Device Programs, Cedars Sinai Medical Center, Los Angeles

Robert McDonough
Head of Clinical Policy Research & Development
Aetna

Brian Mittman
Research Scientist III, Research & Evaluation
Kaiser Permanente Research
Senior Advisor, Veterans Affairs Center for Implementation Practice and Research Support, Los Angeles, CA
Consultant, University of California, Los Angeles, Institute for Innovation in Health
Senior Advisor, RAND Health

Jane Perlmutter
President and Founder
Gemini Group

Alexandra Shields
Associate Professor, Harvard Medical School and Massachusetts General Hospital (MGH)
Director, Harvard/MGH Center on Genomics, Vulnerable Populations, and Health Disparities

SESSION II: EXPLORING MODELS FOR IMPROVING IMPLEMENTATION WHILE GENERATING EVIDENCE IN CLINICAL SETTINGS

Objective: To explore case studies where implementation in clinical care has had varying degrees of success in achieving practice change

Moderator: Catherine Wicklund, Past President, National Society of Genetic Counselors
Director, Graduate Program in Genetic Counseling, Northwestern University

11:30 a.m. **Approaches to Implementation**
Edward Kim
Chair, Solid Tumor Oncology and Investigational Therapeutics and the Donald S. Kim Distinguished Chair for Cancer Research
Levine Cancer Institute, Carolinas HealthCare System

Mary Norton
Professor of Obstetrics, Gynecology, and Reproductive Sciences
University of California, San Francisco

Stephen Kimmel
Professor of Medicine
University of Pennsylvania School of Medicine

12:20 p.m. **Discussion with Speakers, Reactants, and Attendees**
Speakers
Edward Kim
Mary Norton
Stephen Kimmel

Reactants
Bernice Coleman
Robert McDonough
Brian Mittman

Jane Perlmutter
Alexandra Shields

1:00 p.m. **WORKING LUNCH**

SESSION III: POPULATION HEALTH AND GENOMICS: INCREMENTAL IMPLEMENTATION OR RADICAL REFORM?

Objectives: To explore effective strategies and infrastructure that facilitates implementation and how these could be applied to advance the future of genomic medicine

Moderator: Greg Feero, *Workshop Co-Chair*; Associate Editor, *Journal of the American Medical Association*; and Faculty, Maine Dartmouth Family Medicine Residency Program

2:00 p.m. Deb Duquette
Genomics Coordinator
Michigan Department of Health and Human Services

Marc LePage
President and Chief Executive Officer
Génome Québec

Toni Pollin
Associate Professor, Medicine
University of Maryland School of Medicine

2:50 p.m. **Discussion with Speakers, Reactants, and Attendees**
Speakers
Deb Duquette
Marc LePage
Toni Pollin

Reactants
Bernice Coleman
Robert McDonough

Brian Mittman
Jane Perlmutter
Alexandra Shields

3:30 p.m. **Break**

SESSION IV: ACHIEVING THE VISION

Objectives: To reflect on the potential value of implementation science to the translation of genomics to achieve improved health outcomes. To provide concrete examples of how integration of principles of implementation science might accelerate the translational pipeline now and over the next 5–10 years.

Moderator: Debra Leonard, *Workshop Co-Chair*; Professor and Chair of Pathology and Laboratory Medicine, University of Vermont Medical Center

3:45 p.m. **Stakeholder Reaction Panelists**

Health Care Provider Perspective
Bernice Coleman

Payer Perspective
Bob McDonough

Patient Perspective
Jane Perlmutter

Health Disparities Perspective
Alexandra Shields

4:20 p.m. **Discussion with Reactants and Attendees**

5:00 p.m. **Concluding Remarks**
Summary of Important Points and Potential Approaches to Genomic Medicine Implementation

David Chambers
Deputy Director for Implementation Science
National Cancer Institute

5:20 p.m. **Adjourn**

Greg Feero, *Workshop Co-Chair*
Associate Editor, *Journal of the American Medical Association*; Faculty, Maine Dartmouth Family Medicine Residency Program

Debra Leonard, *Workshop Co-Chair*
Professor and Chair of Pathology and Laboratory Medicine
University of Vermont Medical Center

B

Speaker Biographical Sketches

David Chambers, D.Phil., is the deputy director for implementation science in the Division of Cancer Control and Population Sciences, National Cancer Institute, where he manages a team focusing on efforts to build and advance the field of implementation science through funding opportunity announcements, training mechanisms, dissemination platforms, and the enhancement of partnerships and networks to integrate research, practice, and policy.

From 2008 through the fall of 2014, Dr. Chambers served as chief of the Services Research and Clinical Epidemiology Branch (SRCEB) of the Division of Services and Intervention Research at the National Institute of Mental Health (NIMH). He arrived at NIMH in 2001, brought to the institute to run the Dissemination and Implementation Research Program within SRCEB, where he continues to manage a portfolio of grants for studying the integration of scientific findings and effective clinical practices in mental health within real-world service settings. From 2006 to the fall of 2014, Dr. Chambers also served as associate director for dissemination and implementation research, leading National Institutes of Health (NIH) initiatives on the coordination of dissemination and implementation research in health, including a set of research announcements across 15 of the NIH institutes and centers, annual scientific conferences, and a summer training institute.

Prior to his arrival at NIH, Dr. Chambers worked as a member of a research team at Oxford University, where he studied national efforts to implement evidence-based practice within health care systems. He publishes on strategic research directions in implementation science and serves as a plenary speaker at numerous scientific conferences. He received his A.B. degree (with honors) in economics from Brown Univer-

sity in 1997, and an M.Sc. and a D.Phil. degree in management studies (organizational behavior) in 1998 and 2001, respectively, from Oxford University (UK).

Bernice Coleman, Ph.D., ACNP-BC, FAHA, FAAN, is a nurse scientist and nurse practitioner in the Heart Transplantation and Mechanical Circulatory Support (MCS) Programs at Cedars Sinai Medical Center. She has 25 years of experience as an advanced practice nurse caring for patients and families of patients with advanced heart disease.

As a clinician nurse scientist, her research was motivated by observations of disparity in survival after heart transplantation between African American and caucasian American recipients. She recently explored the role of inflammatory genes and their impact upon ethnic outcomes after transplantation. The findings from this research have demonstrated mutually exclusive candidate genes predictive of poor survival for African Americans compared to caucasian Americans after heart transplantation. The translation of genetics and genomics into practice will only be accomplished once care providers have the knowledge and appreciation of the powerful relevance "omics" as potential for changing outcomes.

Dr. Coleman holds a master of science degree from the Yale School of Nursing and a Ph.D. from the University of California, Los Angeles, School of Nursing. Her postdoctoral work was conducted in the Histocompatibility Laboratory at Cedars Sinai Medical Center and the NIH/National Institute of Nursing Research (NINR) Summer Genetics Institute. She has made numerous leadership contributions in professional organizations such as the International Society of Heart and Lung Transplantation, American Heart Association (AHA) Council on Cardiovascular Nursing and Stroke, American Association of Critical Care Nurses, and the Academy of Nursing, and she served as AHA chair of the Western States Affiliates. She currently serves as a member of the U.S. Department of Health and Human Services Advisory Committee on Organ Transplantation.

Debra Duquette, M.S., C.G.C., has served as a project manager/director on two Centers for Disease Control and Prevention (CDC) Office of Public Health Genomics cooperative agreements and three CDC Division of Cancer Prevention and Control cooperative agreements with the Michigan Department of Health and Human Services for public health genomics over the past 11 years. She is also the founder and chair of the Lynch Syndrome Screening Network, which is a consortium of more

than 100 institutions working to promote universal screening for Lynch syndrome on all newly diagnosed colorectal and endometrial cancers. Since 2005 she has served as the project manager for the Michigan Sudden Cardiac Death of the Young Surveillance and Prevention project, and she has facilitated the Michigan Alliance for Prevention of Sudden Cardiac Death of the Young. She serves on the executive steering committee for the Patient-Centered Outcomes Research Institute (PCORI)-funded American BRCA Outcomes & Utilization of Testing Network, on the advisory board of Facing Our Risk of Cancer Empowered, on the Institute of Medicine Ovarian Cancer Research Committee, and on the steering committee of eXamining Relevance of Articles for Young Survivors. She is a board-certified genetic counselor with more than 12 years of clinical experience, specifically counseling more than 8,000 Michigan families, giving her unique insight regarding clinical genetics and public health genomics.

William A. (Andy) Faucett, M.S., L.G.C., is the director of policy and education in the Office of the Chief Scientific Officer at Geisinger Health System and an investigator II in the Genomic Medicine Institute and the Autism and Developmental Medicine Institute. He directs community engagement and public education for Geisinger's biobank, the MyCode® Community Health Initiative. His research focuses on oversight of genetic testing, health care provider education, genetic counseling, rare disease test translation, patient registries, and direct-to-consumer genetic testing. He leads the NIH-funded registry for the ClinGen project, GenomeConnect, and the ethical, legal, and social issues aspect of the NIH-funded Clinically Relevant Variant Resource section of ClinGen. He has a B.S. from the Baptist College at Charleston, South Carolina; an M.S. in human genetics from Sarah Lawrence College; and board certification from the American Board of Genetic Counseling. He has held positions at Emory; Baylor College of Medicine; Memorial Medical Center in Savannah, Georgia; and the CDC. He has been a member of The Personal Genome Project since 2009.

W. Gregory Feero, M.D., Ph.D., obtained his M.D./Ph.D. from the University of Pittsburgh School of Medicine's Medical Scientist Training Program with a Ph.D. in human genetics. He then completed his residency in family medicine at the Maine–Dartmouth Family Medicine Residency Program in Augusta, Maine. After 5 years in practice in Maine, Dr. Feero accepted a position at the National Human Genome Research

Institute (NHGRI) of the NIH as a senior advisor to the director for genomic medicine under Dr. Francis Collins and Dr. Alan Guttmacher. In this role, he played a key role in coordinating NHGRI's activities related to family health history and was the planning chair for the NIH Consensus Development Program's 2009 State of the Science Conference "Family History and Improving Health." He also participated in efforts to help ensure the appropriate representation of family health history and genomic data in electronic health records. Additionally, as chief of the Genomic Healthcare Branch in the Office of the Director he oversaw efforts to advance genomics education for health professional disciplines including nurses, physician assistants, physicians, and pharmacists. In 2012, Dr. Feero stepped down from his position at NHGRI and continued on his role as faculty and research director at the Maine–Dartmouth Family Medicine Residency program. Currently he serves on the National Academies of Sciences, Engineering, and Medicine's Roundtable on Translating Genomic-Based Research for Health and as a contributing editor for the *Journal of the American Medical Association*. Dr. Feero sees patients 4 days per week in Fairfield, Maine; is board certified in family medicine; and holds professional licenses in Maine and West Virginia. He has authored numerous peer-reviewed and invited publications.

Edward S. Kim, M.D., is the chair of solid tumor oncology and investigational therapeutics and the Donald S. Kim Distinguished Chair for Cancer Research at the Levine Cancer Institute, Carolinas HealthCare System in Charlotte, North Carolina. Dr. Kim was previously at The University of Texas MD Anderson Cancer Center in Houston, where he was an associate professor of medicine, the chief of the Section of Head and Neck Medical Oncology, and the director of clinical research operations in the Department of Thoracic/Head and Neck Medical Oncology.

Dr. Kim received his bachelor of science and medical degrees from the Honors Program in Medical Education (HPME) at Northwestern University in Chicago, Illinois, in 1996. Dr. Kim completed residency in internal medicine at the Baylor College of Medicine in Houston, Texas, 1996–1999, and his fellowship in medical oncology at The University of Texas MD Anderson Cancer Center, 1999–2001.

Dr. Kim studies novel targeted agents in the treatment and prevention settings and has expertise in lung, head, and neck as well as thymic cancers. He serves as a principal investigator on numerous clinical studies, including the Department of Defense Biomarker-based Approaches

of Targeted Therapy for Lung Cancer Elimination (BATTLE), a personalized medicine program in lung cancer.

Dr. Kim serves as the chair of several national committees, including the American Society of Clinical Oncology (ASCO) Cancer Research Committee, Early Phase Central Institutional Review Board, and International Association for the Study of Lung Cancer (IASLC). He also serves on the editorial boards of *Journal of Clinical Oncology*, *Clinical Cancer Research*, and *Clinical Lung Cancer* and is a member of numerous associations and societies, including ASCO, the American Association for Cancer Research (AACR), SWOG, and IASLC. Dr. Kim is also the recipient of several awards, including the ASCO Young Investigators Award and the AACR Scholar in Training Award. He also has been the recipient of a V Foundation grant and a Department of Defense grant.

Dr. Kim is the author or co-author of more than 100 published articles, book chapters, reviews in journals such as *Lancet*, *Lancet Oncology*, *Journal of Clinical Oncology*, *Cancer Discovery*, *Cancer*, and *Cancer Prevention Research*, involving cancer therapeutics and prevention with chemotherapy and novel targeted agents, with particular emphases on lung cancer and head and neck cancer.

Stephen Kimmel, M.D., M.S.C.E., is a professor of medicine (cardiology) and epidemiology, the director of the Division of Epidemiology and the Clinical Epidemiology Unit, a senior scholar in the Center for Clinical Epidemiology and Biostatistics, a senior fellow of the Center for Behavioral Health Research, a senior fellow of the Leonard David Institute, and a director of the Center for Therapeutic Effectiveness Research (CTER). Dr. Kimmel has performed pharmacogenetic and adherence research for the past 15 years. He was the coordinating center principal investigator (PI) for the Clarification of Optimal Anticoagulation through Genetics (COAG) trial. He is also the founding director of the CTER, which is dedicated to improving the use of existing therapeutics through research that aims to improve medication adherence and our understanding of genetics-based interventions. He is also the PI of the coordinating center for the Implementing GeNomIcs In pracTicE (IGNITE) Network, which was established to enhance and accelerate the use of genomic medicine by incorporating genomic information into clinical care and exploring methods for effective implementation, diffusion, and sustainability.

Debra G. B. Leonard, M.D., Ph.D., is professor and chair of the Department of Pathology and Laboratory Medicine at the University of Vermont Medical Center in Burlington. She is an expert in the molecular pathology of genetic, cancer, and infectious diseases and in policy development for genomic medicine. Her M.D. and Ph.D. degrees were completed at the New York University School of Medicine, where she also did her postgraduate clinical training in anatomic pathology, including a surgical pathology fellowship. She is certified by the American Board of Pathology in anatomic pathology, and by the American Boards of Pathology and Medical Genetics in molecular genetic pathology. Currently, Dr. Leonard is a member of the Roundtable on Translating Genomic-Based Research for Health at the National Academies of Sciences, Engineering, and Medicine, and previously served as a member of the Committee on the Review of Genomics-Based Tests for Predicting Outcomes in Clinical Trials. She is a fellow of the College of American Pathologists (CAP) and the chair of the CAP's Personalized Healthcare Committee. Dr. Leonard is a past member of the Secretary's Advisory Committee on Genetics Health and Society (SACGHS) to Secretary Michael O. Leavitt and a past president and 2009 Leadership Award recipient of the Association for Molecular Pathology. She has spoken widely on various molecular pathology test services, the future of molecular pathology, the impact of gene patents on molecular pathology, and the practice of genomic medicine.

Marc LePage was appointed president and chief executive officer of Génome Québec in December 2011. He brings to the organization a wealth of experience in the innovation sector and venture capital, in addition to a broad network of international contacts. One of his major mandates as president and CEO is to reach new agreements in a bid to diversify sources of funding.

He is an expert in international partnerships and, since 2009, served as special advisor, climate change and energy for the Embassy of Canada in Washington, DC. He previously worked as consul general at the Canadian Consulate in San Francisco/Silicon Valley.

Mr. LePage was also one of the pioneers behind the founding of Genome Canada in 2000. During his tenure as executive vice president of corporate development, he made a significant contribution to the development of genomics in Canada.

From 1994 to 2000, he worked as the director of business development for the Medical Research Council, where he was in charge of build-

ing international partnerships with the pharmaceutical industry, venture capital, and foundations.

Mr. LePage is a member of the board and the governance committee of the Québec Network for Personalized Health Care. He also sits on the board of Canada World Youth.

Robert S. McDonough, M.D., is senior director for clinical policy research and development for Aetna, where he is responsible for developing Aetna's medical policies. He is co-chairman of Aetna's Pharmacy and Therapeutics Committee and chairman of Aetna's Policy and Plan Design Committee. He is a member of the Medicare Evidence Development and Coverage Advisory Committee. He has special interests in preventive health services, technology assessment, and outcomes research.

He is former senior analyst and project director with the health program of the Congressional Office of Technology Assessment. He is a graduate of Duke University School of Medicine and School of Law (J.D.) and has a master's degree in policy analysis from Duke's Sanford Institute of Public Policy. He completed an internship in internal medicine at Stanford University School of Medicine, and is a fellow of the American College of Legal Medicine.

Brian S. Mittman, Ph.D., is a senior scientist at the Veterans Affairs (VA) Center for Implementation Practice and Research Support (Department of Veterans Affairs Greater Los Angeles Healthcare System) and a senior research scientist at the Kaiser Permanente Southern California Department of Research and Evaluation. He has additional affiliations at RAND and at University of California, Los Angeles (UCLA), where he co-leads the UCLA Clinical and Translational Science Institute (CTSI) Implementation and Improvement Science Initiative.

Dr. Mittman convened the planning committee that launched the journal *Implementation Science* and served as co-editor in chief from 2005 to 2012. He was a member of the Forum on the Science of Quality Improvement and Implementation at the National Academies of Sciences, Engineering, and Medicine, and chaired the NIH Special Emphasis Panel on Dissemination and Implementation Research in Health in 2007 and 2010. He directed the VA's Quality Enhancement Research Initiative (QUERI) from 2002 to 2004 and established the VA QUERI implementation research "resource center," the Center for VA Implementation Research and Practice Support, in 2008. He currently serves on the Methodology Committee for PCORI, the Association of American Med-

ical Colleges Advisory Panel on Research, the AcademyHealth Methods Council and Education Council, and on advisory boards for several additional research programs in implementation science in the United States and abroad.

Mary Norton, M.D., is a professor of obstetrics, gynecology, and reproductive sciences at the University of California, San Francisco, and vice chair of clinical and translational genetics and genomics in her department. She is a practicing perinatologist and clinical geneticist and is board certified in maternal fetal medicine as well as clinical genetics. She has been involved in clinical research and clinical trials throughout her academic career and has particular interest in studies focused on pregnancy, prenatal diagnosis, and perinatal genetics.

Her experience in clinical research is extensive and varied, and she has collaborated in numerous multi-center trials. She was the principal investigator (PI) of the Maternal Fetal Medicine Network site at Stanford University, which she implemented at that center. She recently completed a multicenter trial of cell-free DNA for prenatal aneuploidy detection. This was an international study involving numerous sites that recruited more than 18,000 participants in just over 1 year; the primary manuscript was published in the *New England Journal of Medicine*. She was also a co-investigator for another recently completed National Institute of Child Health and Human Development–sponsored multicenter trial as the primary co-PI; the primary manuscript was published in *JAMA* and focused on patient education and decision making surrounding prenatal genetic testing. She has been, or currently is, on several national committees that are involved in national guidelines regarding genetic testing, including the American Congress of Obstetricians and Gynecologists Committee on Genetics and the Society for Maternal–Fetal Medicine publications committee. She is the president-elect of the Society for Maternal–Fetal Medicine and the current president of the Perinatal Quality Foundation, two important societies working actively in the promotion of quality maternal fetal care. She has completed several studies in collaboration with the California Genetic Disease Screening Program as well as with Kaiser Permanente.

Jane Perlmutter, Ph.D., M.B.A., is a long-term cancer survivor and has been involved in a number of organizations committed to educating the public on cancer, supporting people affected by it, and eradicating the disease. She is an advocate representative in several clinical trials con-

sortia, multi-institutional grants, clinical guideline committees, grant review panels, National Cancer Institute steering and working groups, Innovation in Medical Evidence Development and Surveillance steering committee, PCORI patient engagement advisory panel, and Committee on Policy Issues in the Clinical Development and Use of Biomarkers for Molecularly Targeted Therapies at the National Academies of Sciences, Engineering, and Medicine. She has also been an active member of the Clinical Trials Transformation Initiative. She is especially committed to training less experienced patient advocates, has written articles and tutorials on this topic, and is often involved in advocate training.

Dr. Perlmutter has a Ph.D. in cognitive psychology and master's degrees in educational psychology and computer and information science as well as an M.B.A. She started her career as an experimental cognitive psychologist at the University of Texas in Austin and spent most of her career at Bell Labs. She has run the Bell Technical Training Center and held an officer position in DeVry Inc., a publicly traded for-profit higher education company. She currently runs her own consulting company—Gemini Group. Her consulting focuses on process improvement for small businesses, not-for-profits, and institutions of higher learning.

Toni Pollin, Ph.D., is a human geneticist and board-certified genetic counselor. Her research interests lie in mapping genes involved in susceptibility to type 2 diabetes and related complications, particularly related to lipids and cardiovascular disease, and clinical translation of emerging genetics findings into clinical uses. Her current major research efforts involve an National Human Genome Research Institute–funded implementation study of a program designed to screen for, diagnose, and promote individualized therapy for highly penetrant genetic forms of diabetes; studying gene x lifestyle/pharmaceutical interactions in the Diabetes Prevention Program (a multi-center, multi-ethnic clinical trial showing reduction in diabetes incidence using metformin or intensive lifestyle changes); characterizing the metabolic and cardioprotective effects of inborn apolipoprotein C-III deficiency resulting from a founder mutation in the Old Order Amish; and the genetics and pharmacogenetics of diabetes in children and adolescents in the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) Study. She also leads the Amish Wellness Study, a study designed to assemble a community-based Amish biobank while providing basic health screening to the Lancaster Amish population, and provides genetic analysis

expertise to colleagues across campus. She has published more than 70 peer-reviewed articles and several book chapters and review articles.

Dr. Pollin teaches formally in the graduate school, medical school, and genetic counseling training program at the University of Maryland School of Medicine and provides research mentorship to students in these programs along with undergraduate students, clinical and postdoctoral fellows, and junior faculty. She is actively involved in the education of genetic and other health care providers regarding the genetics of diabetes at both the local and national levels, having lectured on the subject to the National Society of Genetic Counselors, American Diabetes Association, and physicians, nurses, and geneticists at the university and other hospitals in the Baltimore area. Finally, she serves on the NIH Clinical and Integrative Cardiovascular Sciences Scientific Review Group, American Diabetes Association Research Grant Review Committee, and National Society of Genetic Counselors Practice Guidelines Committee, and she has been an invited participant in several NIH workshops related to genetics and genomic medicine and research.

Alexandra Shields, Ph.D., is the director of the Harvard/Massachusetts General Hospital (MGH) Center on Genomics, Vulnerable Populations, and Health Disparities; an associate professor of medicine at the Harvard Medical School; an associate in health policy at MGH; and associate faculty in molecular and population genetics at the Broad Institute. Dr. Shields' work addresses the challenges of clinical integration of new genomic medicine and technologies into clinical practice, with a particular focus on the impact of these changes on minority and underserved populations. She has conducted several national surveys addressing the preparedness of primary care physicians to incorporate genomic medicine into practice more generally, access to established genetic tests at safety net provider sites, and consumers' willingness to undergo genetic testing. Dr. Shields also studies important ethical aspects of genomics research design, including the use of race constructs in genomics research and the inclusion of environmental measures most important to understanding health disparities in gene–environment interaction studies. Dr. Shields has authored more than 40 peer-reviewed publications; co-directs the Health Disparities Research Program of the Harvard Clinical and Translational Science Center; is an executive committee member of the Dana-Farber/Harvard Cancer Center's Reduction of Cancer Risk and Disparities Program; and serves on advisory boards of several National Institutes of Health and university-based research initiatives addressing genomics

and health disparities. She holds a Ph.D. in health policy from Brandeis University, where she was a Pew Health Policy Scholar, as well as a B.A. (summa cum laude, Phi Beta Kappa) and an M.A. (with distinction) in systematic theology from Boston College.

Consuelo H. Wilkins, M.D., M.S.C.I., is the executive director of the Meharry–Vanderbilt Alliance, a strategic partnership between Meharry Medical College and Vanderbilt University School of Medicine. Her primary responsibilities include developing and supporting collaborative initiatives and programs in biomedical research, community engagement, and interprofessional learning. She holds appointments as an associate professor of medicine at both Vanderbilt University School of Medicine and Meharry Medical College. As co-director of the Meharry–Vanderbilt Community Engaged Research Core in the Vanderbilt Institute for Clinical and Translational Science, she brings together academic researchers and community members to improve community health and health care through community-engaged research. Dr. Wilkins is widely recognized for her work in stakeholder engagement and is the principal investigator of a PCORI research award focused on improving patient engagement and understanding its impact on research.

Dr. Wilkins' prior research has focused on understanding the complex intersection between cognitive impairment, frailty, and depression. Prior to joining the faculty at Vanderbilt University Medical Center in 2012, Dr. Wilkins was an associate professor in the Department of Medicine, Division of Geriatrics, with secondary appointments in psychiatry and surgery (public health sciences) at Washington University School of Medicine in St. Louis. She served as founding director of the Center for Community Health and Partnerships in the Institute for Public Health, co-director of the Center for Community Engaged Research in the Clinical and Translational Science Awards (CTSA) consortium, and director of Our Community, Our Health, a collaborative program with Saint Louis University to disseminate culturally relevant health information and facilitate community-academic partnerships to address health disparities.

Dr. Wilkins serves on numerous national committees and boards, including the CTSA Consortium Collaboration/Engagement Domain Task Force (lead team); PCORI Advisory Panel on Clinical Trials Subcommittee on Recruitment, Accrual, and Retention; PCORnet Patient and Consumer Engagement Task Force (co-chair); and the National Institute on Aging Task Force for Diversity in Scholar Development in Aging/Neurocognitive Disease and Research Recruitment.

Dr. Wilkins earned a bachelor of science in microbiology (magna cum laude, Phi Beta Kappa) and a doctor of medicine from Howard University. She completed residency training in internal medicine at Duke University Medical Center and a geriatric medicine fellowship at Washington University School of Medicine/Barnes-Jewish Hospital. Following her medical training, Dr. Wilkins earned a master of science in clinical investigation from Washington University School of Medicine.

C

Statement of Task

An ad hoc planning committee will organize and conduct a public workshop to examine how the implementation of novel technology in health care and lessons from prior adoptions can be applied to genomic medicine advances. A variety of examples in health care may be considered, including the adoption of electronic health records or the introduction of imaging and other technologies. The workshop goal will be to learn from existing examples and examine the challenges, opportunities, and best practices to implementing genomic technologies in the health care system without exacerbating health care disparities. A diverse stakeholder group, which may be composed of health care system leadership, clinical providers, patients, implementation science experts, and others, will be invited to present their experiences and perspectives. The planning committee will develop the workshop agenda, select speakers and discussants, and moderate the discussions. An individually authored summary of the workshop will be prepared by a designated rapporteur in accordance with institutional policy and procedures.

D

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E

Implementation Science: A Background[1]

OVERVIEW

For years, a major priority for researchers and health professionals has been working toward the triple aim of health care—increased access, lower costs, and better outcomes. A relatively new field, implementation science (collectively referred to as dissemination and implementation science) seeks to bring new tools to the table to help achieve those goals. At its most basic level, implementation science is used to evaluate the methods of influencing systematic changes to routine care using evidence-based practices (EBPs) (Eccles and Mittman, 2006). Evaluation involves looking at barriers and opportunities to provide solutions that maximize benefits across the system. Although the integration of research into practice is not a new concept, the need for carefully evaluated and constructed implementation methods is becoming increasingly more common. For example, in 2010 an estimated $550 billion could have been saved in the U.S. health system had effective implementation methods been used (IOM, 2010). New technologies such as genomic sequencing and the use of big data through electronic health records (EHRs) and mobile health applications have enormous potential to improve health outcomes and reduce cost if implemented successfully in the clinic, but they also have their own challenges and implications. For instance, certain tools that have been implemented, such as advanced imaging, have proven to be successful, but they are also raising questions regarding their effectiveness and economic value (IOM, 2010). As

[1]This background paper was prepared by Roundtable staff member, Meredith Hackmann, and shared with the participants in advance of the workshop.

genomics moves from the research to the clinical space, applying an implementation science approach may be considered if the goal is to reduce gaps among quality, cost, and health.

Terms and Methods

The main approaches or methods to implementation are diffusion and dissemination. Whereas diffusion is passive, dissemination uses active strategies based on how and what the intervention is aiming to achieve (Rabin et al., 2008). Although diffusion has been the dominant approach for implementing new EBPs, more and more implementation work is focusing on dissemination. Rogers (2003) illustrates diffusion as a bell curve with five different categories of adopters based on certain behavioral traits. Much like social media, there are "innovators" and "early adopters" at the beginning who tend to be thought leaders and open to new ideas, followed by "early majority" and "late majority," who will adopt after there is evidence of success, and finally "laggards," who tend to be more conservative and will not adopt until there is significant evidence or pressure from others (Rogers, 2003).

One challenge in implementation science is the lack of consensus concerning terminology (Damschroder et al., 2009; Tabak et al., 2012), which arguably makes identifying methods and research strategies difficult. Some of the most common terms used in implementation science are *adaptation/reinvention*, or how an intervention changes during adoption; *feasibility*, the probability of an intervention succeeding; and *sustainability*, or how well implementation is maintained over time (Proctor et al., 2011; Rabin et al., 2008; University of Colorado, 2015). Adaptation/reinvention, feasibility, and sustainability all depend heavily on the context, or setting, of an intervention. While there are numerous methods for dissemination and implementation research, Tabak et al. (2012) group the methods into three categories: construct flexibility, which scores the adaptability of an approach on a scale from 1 to 5 where 1 = broad and 5 = operational; dissemination and/or implementation, which defines a method by the extent to which it focuses on dissemination, implementation, or both equally; and a socio-ecological framework, which categorizes methods according to level at which they operate (e.g., individual, organization, community, or system).

Implementation Challenges

In the context of the rapid learning health care concept discussed by Charles Friedman (IOM, 2015), the current system is ineffective at feeding the translation of data back into the system to improve future care and research. Rather than learning from what does not work, the system is sluggish and continues in the same cycle, with most of the data sharing occurring in the form of journal publications. Here, applying the principles of implementation science may have potential for improving the system.

Manojlovich et al. (2015) argue that implementation often places too much emphasis on evidence when more focus needs to be on how various groups can come to a collective understanding or, in other words, how they achieve knowledge translation. This is perhaps one of the biggest gaps and one of the most important to address as further funding is allocated to comparative effectiveness research. Too often, research stops after the evidence is generated, with little regard given to how best to roll out an intervention in a given setting (Glasgow et al., 2012).

Part of the issue may be a lack of research funding, instead of a lack of awareness. The National Institutes of Health (NIH) spends roughly $30 billion on basic research and discovery per year; by comparison, the Agency for Healthcare Research and Quality spent $270 million on research related to dissemination and implementation in 2010, or 0.9 percent of the total amount spent on discovery (Glasgow et al., 2012). To further complicate the matter, only 14 percent of research is ever fully put into practice and of that 14 percent it takes an average of 17 years for the research to be fully realized in practice (Balas and Boren, 2000). However, with the creation of the Patient-Centered Outcomes Research Institute in 2010 and the NIH Collaboratory in 2015, high-quality efficacy research and demonstration projects may now be moving the field forward.

Potential Opportunities for Implementation

Implementing EBPs into routine care is a significant challenge, with one of the most important factors in adoption success being organizational culture and behavior. When the implementation of EBPs is supported on multiple levels of an organization, there tend to be higher rates of success (Aarons et al., 2015). As expected, tailored planning based on the context of an intervention is an important consideration and offers

significant opportunities for leadership. Many interventions fail simply as a result of poor planning for an intended target setting (Glasgow and Emmons, 2007). On an organizational level, the interviews with institutional leadership completed by the Roundtable on Translating Genomic-Based Research for Health found, perhaps unsurprisingly, that centralized systems and institutional policies that required compliance had greater success in implementing new practices.

Health system leadership plays a significant role in the success of EBP adoption. While implementing more efficient methods and technologies has great potential for reducing costs and increasing value to the overall health care system, individual systems can face more constraints, particularly financial ones. For instance, it is estimated that $77 billion could be saved annually if 90 percent of health care providers adopted an EHR system, though the majority of providers investing in that system will not see those cost-savings (Balfour et al., 2009). On the other hand, research also suggests that cost-effectiveness does not always lead to an EBP being implemented into practice (Clark et al., 2013).

The role of regulatory agencies could also be considered. In the United States, basic EHR adoption by nonfederal acute hospitals was 9.4 percent in 2008, but the major uptake after 2009 (from 15.6 percent to 59.4 percent) was due in part to the Health Information Technology for Economic and Clinical Health (HITECH) Act passed by Congress, which encouraged EHR implementation through incentives and grants (Charles et al., 2014). In that way, non-academic health centers and smaller systems have been able to participate as well. In comparison with the United States, many countries with more centralized health systems tend to have higher rates of EHR adoption (Balfour et al. 2009).

Implementing New Technologies

Implementing new technology shares many of the hurdles of implementing EBPs. Across industry, it takes an average of 15 years for a new technology to be fully implemented (RAND, 2005). In the case of laparoscopic surgery,[2] for example, adoption has become more widespread for certain procedures, such as cholecystectomies and colectomies. A large part of the success of laparoscopy in these areas has come as a re-

[2]Other examples of technology for comparison not explored here may be positron emission tomography (PET) scanning, robotic surgery, smart infusion pumps, bladder scanners, VeinVue, wound vacuum-assisted closure (VAC), the use of Extracorporeal Membrane Oxygenation (ECMO), and telehealth.

sult of the medical benefits realized by patients and the financial benefits realized by health systems (NIH, 1992).

Laparoscopic cholecystectomy, a camera-guided removal of the gallbladder performed through a small incision (as opposed to open cholecystectomy, an open abdominal surgery to remove the gallbladder) began being implemented in the late 1980s. It was estimated that gallstones cost the health system $5 billion annually, with the majority of the cost coming from the long length of hospitalization required for an open cholecystectomy (NIH, 1992). In this particular case, the technology was quickly adopted, and implementation occurred very quickly because of the lack of perceived deterrents and a surplus of patient support. By 1992, the adoption rate was estimated to be 80 percent, and an NIH consensus panel had placed its seal of approval on the procedure, citing decreased pain and disability as two major benefits for patients (Allori et al., 2010; NIH, 1992). Furthermore, the cost-effectiveness of the surgical procedure was touted since it reduced post-operative complications. One of the interesting aspects of implementation was the limited research that supported the operation's use. Clinicians eagerly adopted the procedure, seeing only benefits for patients. Because of high patient demand, research data supporting the comparative effectiveness was limited and became difficult to justify after widespread use (Allori et al., 2010; NIH, 1992).

Laparoscopic colectomy, which removes all or part of the colon through a small incision using a camera, has not had such high rates of adoption, but its use has nonetheless been growing steadily since its first implementation in the early 1990s (Bardakcioglu et al., 2013). Despite the fact that evidence from randomized trials has in this case shown benefits for patients, the adoption rate was only 31.4 percent in 2009, up from 5 percent in 2004 (Bardakcioglu et al., 2013). Of course there are other considerations with a laparoscopic colectomy—mainly that it is a more difficult procedure and has other complications that must be considered. Surgeons cite the lengthy learning process as one of the biggest impediments to its adoption (Luglio et al., 2015; Moloo et al., 2009). In addition, certain financial and socioeconomic factors have played into adoption. For instance, Bardakcioglu et al. (2013) found that private insurance was a positive factor for use of the laparoscopic procedure, while factors such as being a minority and having a low economic status were negative factors in adoption, raising important questions about the potential for new and beneficial technology to create health disparities.

Possible Prospects for the Future

With genomic medicine in its early stages, there may be opportunities to apply the principles of implementation science to inform best practices and facilitate adoption. In the context of genomics, some of the challenges may be different, but certain evidence constraints and complexities faced by large health systems have been encountered in other implementation efforts and offer learning potential for the field. Perhaps one of the lessons learned from the implementation of laparoscopic technology is that one of the key areas for engagement and effective communication could be in working with patients and consumers. As health care increasingly moves toward a patient-centric model with patients having more of a voice in their treatment options, the demand for new health technologies will likely grow. Nilsen (2015) suggests that more research should focus on how these end users impact implementation outcomes. Quality improvement for patients also means looking at the possibility that these new technologies might exacerbate health care disparities, which will require learning how to mitigate them. From the gaps explored in implementation science, it seems that a multi-stakeholder approach may provide a unique opportunity to bring about improved health and lasting change for the health care system.

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F

Large Genetic Cohort Studies: A Background[1]

BACKGROUND

For decades, large-scale prospective studies have been carried out with the goal of accurately assessing the relationships between biomedical factors, environmental exposures, and health outcomes for both their study participants[2] and source populations (Willett and Colditz, 1998). For example, extensive personal data collected for the National Health and Nutrition Examination Survey (NHANES) led to the discovery of the association between high cholesterol levels and heart disease,[3] while the Framingham Heart Study made clear the heart health risks of tobacco smoking.[4] Recently, technological advancements have opened the door for the incorporation of genetic data into these types of studies, allowing for the discovery of specific pathogenic and protective genotypes through genome-wide association studies (GWASs).

[1]This background paper was prepared by Roundtable interns during the summer of 2015, Andy Castro (Northwestern University) and Lauren Nahouraii (Duke University), and shared with the participants in advance of the workshop.

[2]The use of the terms "cohort" and "participant" are currently being reconsidered by the genetics research community, but since there is no current consensus on an alternative, these were the terms chosen for use in this article.

[3]National Health and Nutrition Examination Survey, http://www.cdc.gov/nchs/nhanes.htm (accessed June 13, 2016).

[4]Framingham Heart Study, https://www.framinghamheartstudy.org (accessed June 13, 2016).

Using genetic data in studies like NHANES and the similar Wisconsin Longitudinal Study[5] has been advantageous because of the large volume and various types of phenotypic information on record for comparison. Similar methods allowed the Framingham Heart Study to find added success in identifying pathogenic variants and confirming the functions of candidate genes (Framington Heart Study, 2016). Seeing the potential of this model for drug development, pharmaceutical companies have started collaborating with organizations that have access to large databases of genomic information. For example, 23andMe's partnership with Genentech seeks to find a genetic cause of Parkinson's disease by using data from 600,000 consenting customers, and Amgen's acquisition of DeCode Genetics allows access to data for over half of Iceland's adult population (Chen, 2015). Similarly, Geisinger Health System has partnered with Regeneron to sequence and research 100,000 participants as part of its MyCode Community Health Initiative.

Other countries have begun longitudinal research using genomic and other data as well, using centralized systems like the UK Biobank (Manolio et al., 2012), Qatar Biobank,[6] and Danish Civil Registration System (Schmidt et al., 2014). These offer examples of how other countries' health care infrastructures may allow researchers easier and less expensive access to linked biomedical information because the information can all be found in one place. Alternatively, less centralized consortium models can compile data from similar studies, such as the National Cancer Institute's Cohort Consortium, which unites more than 40 cohorts consisting of more than 4 million people,[7] and the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE), which performs meta-analyses and GWASs for 10 separate cohorts.[8] The Precision Medicine Initiative (PMI) of the National Institutes of Health (NIH) may adopt the consortium method in part by incorporating ongoing studies with direct volunteer recruitment, pursuing a goal of enrolling over 1 million Americans (Collins and Varmus, 2015). The scale and scope of new endeavors in large cohort research may provide an opportunity to learn from previous and ongoing studies.

[5]Wisconsin Longitudinal Study, http://www.ssc.wisc.edu/wlsresearch/gwas (accessed June 13, 2016).

[6]Qatar Biobank for Medical Research, http://www.qatarbiobank.org.qa (accessed June 13, 2016).

[7]National Cancer Institute Cohort Consortium, http://epi.grants.cancer.gov/Consortia/cohort.html (accessed June 13, 2016).

[8]Cohorts for Heart and Aging Research in Genomic Epidemiology, http://www.charge consortium.com, (accessed June 13, 2016).

Public Support and Willingness to Participate

The success of large genetic cohort studies relies on the enrollment and retention of participants, and achieving this may be aided by understanding and responding to public perception about participation. Research by Kaufman et al. (2008) found that among a representative sample of 4,659 Americans, 84 percent supported conducting genetic research, and 60 percent said they would participate. This was consistent across most racial/ethnic demographics, with only American Indian/Alaskan Native respondents showing relatively less support (65 percent). Similar surveys have shown that participant support may be directly correlated with both education and income level. These surveys also show significantly higher approval among urban respondents (80 percent) than rural respondents (73 percent) and a higher likelihood of participation among Spanish speakers (61 percent) than English speakers (56 percent) (Bollinger et al., 2014; Kaufman et al., 2008; PMI Working Group, 2015).

Kaufman et al. (2008) assessed what factors would incentivize participation in a large genetic cohort study and found that the return of individual results had the most positive impact on recruitment. Ninety percent of participants desired the return of all of their results, even if they offered no clinical utility (Kaufman et al., 2008). More recent surveys support these findings, with 82 percent of respondents in one study indicating "it would be interesting to receive the results of the study" (PMI Working Group, 2015) and 90 percent indicating that "learning information about [their] health" was either somewhat or very important in influencing their decision to participate (Bollinger et al., 2014).

The public's clear interest in receiving individual data and health information could be seen as challenging by some researchers, as the process of returning results is costly and time consuming and can be bound by institutional review board restrictions. There may also be a notion among researchers that they should "protect" participants from possible misconceptions regarding the therapeutic value of research data (Bollinger et al., 2014; Kaufman et al., 2008). However, Bollinger et al. (2014) showed that if participants are informed of the fact that the return of results may slow the progress of a study, participants become more willing to compromise and accept only medically actionable information. This could indicate a "middle ground" that is palatable to both participants and researchers for future large-cohort studies. MyCode plans to return results on genetic variants that have been identified as actionable

by the American College of Medical Genetics and Genomics, and patients will then be referred to precision health clinics for appropriate genetic counseling.

Additionally, both the Kaufman et al. (2008) research and a survey presented by the PMI Working Group (2015) identified monetary compensation as the second most important incentive for participation, with 80 percent of respondents ranking it as either somewhat or very important. Kaufman et al. (2008) found no difference in the effect of a $200 incentive on participation rates between those earning less than $25,000 per year and those earning more than $75,000 per year. A review of population-based cohort studies also showed that increasing monetary incentives had the largest positive effect on the retention rates of participants (Booker et al., 2011).

Use of Modern Technology in Recruitment and Data Collection

Using various technological innovations may help in enrolling and following up with study participants. The Kaiser Research Program on Genes, Environment, and Health and the Vanderbilt University BioVU program use models of recruitment for cohort studies that are built into their existing electronic health record and patient registries, allowing for a simpler linkage of information and follow up. However, differences in medical terminology can cause confusion when medical histories are being assessed, and many institutions do not currently possess the technological infrastructure to support interoperability (Manolio et al., 2012). Other methods of recruitment using e-mail and text messaging services have been shown to be cost-effective and popular with younger participants, but they produce lower response rates than mailed requests. The use of social media is an inexpensive, though time-consuming, method to inform and update participants on recent developments, and it allows the participants to promote the study they are involved in and encourage their friends and family to participate as well (Toledano et al., 2015). A survey of participants in the Qatar Biobank showed that 72 percent decided to contribute based on recommendations from friends and family, demonstrating the influential power of "word of mouth" on recruitment (Qatar Biobank, 2015).

The European Prospective Investigation into Cancer and Nutrition (EPIC) study has experienced success in recruitment and data collection by using touch-screens instead of interviews or paper forms (Manolio et al., 2012). 23andMe has employed a user-friendly interface for its web-

site that prompts the user with questions about his or her health history.[9] Similarly, the collection of large amounts of various types of biomedical data from wearables (e.g., Fitbit, Apple Watch) and smartphones offers new ways to engage the public. While the specifics of how to effectively implement these technologies are still being studied, 60 percent of respondents to the 2015 NIH survey said that, given the opportunity, they would use a mobile device to submit health data at least once a day (PMI Working Group, 2015).

Consent, Data Sharing, and Privacy

It is generally difficult during the initial consent process of a large-cohort study to foresee what sorts of future studies might also use the data collected for that study. Thus, researchers who conduct such studies generally prefer to use broad consent models as a way of reducing the financial and time costs of re-consenting participants (NHGRI, 2005). While 64 percent of respondents to the 2015 PMI survey mentioned above said they would give broad consent, 73 percent said that they would prefer a dynamic model that would allow personal control over exactly who could use their data and how. "Layered" or "tiered" consent models ensure that participants are informed of their options, but the process can be time-consuming for clinicians and researchers.

To alleviate this problem, innovative models like Genetic Alliance's Platform for Engaging Everyone Responsibly (PEER)[10] are being implemented. PEER is an online, user-friendly interface that educates research participants about the practices and goals of individual studies so that they can selectively decide who can access their data and for what purposes. Users also determine their own privacy settings by either keeping their data anonymous or allowing it be linked back to them for use in clinical care. Models similar to PEER could be useful in streamlining the consent process while empowering participants to take control of their health data.

[9]23andMe Research Portal, https://www.23andme.com/23andMeResearchPortal (accessed June 13, 2016).

[10]Platform for Engaging Everyone Responsibly, http://www.geneticalliance.org/programs/biotrust/peer (accessed June 13, 2016).

Engagement of Health Care Providers

The main obstacles that physicians cite as preventing them from participating in research and engaging their patients are: research that does not fit their practice, high work burden/pressure, and unfamiliarity with the study (lack of understanding of research objectives) (Arends et al., 2014). Within the current health care reimbursement restructuring, physicians also lack the time to devote to studies (Robitaille et al., 2014).

Physicians also perceive barriers to integrating genetics services, which may in turn hamper the recruitment of the physicians' patients to participate in scientific research. Some of the barriers that have been identified are a lack of genetic knowledge and skills; ethical, social, and legal implications (ESLIs); health care system inadequacies; and lack of scientific evidence (Mikat-Stevens et al., 2015). In addition, there is a lack of awareness among primary care physicians about the Genetic Information Nondiscrimination Act, which was passed in 2008 to prohibit the use of genetic information in health insurance and employment. If physicians remain skeptical about the potential of personal genetic information to negatively affect patients' insurability or further coverage, they are unlikely to recruit their patients for research (Mikat-Stevens et al., 2015).

Robitaille et al. (2014) designed a systematic process for recruiting physician–patient dyads in practice-based research networks (PBRNs) and found that there are two main components of successfully recruiting physicians—a personal connection and participant buy-in. Additionally, Long et al. (2014) showed that physicians who work in clinical units where colleague physicians recruit participants are more likely to recruit participants themselves. Peer coaching by "physician champions" could be a valuable avenue of not only recruiting clinicians but also keeping them engaged and recruiting patients (Long et al., 2014).

Addressing Potential Disparities and Building Trust

Discrepancies in health status and care among racial/ethnic groups are well documented (Lavizzo-Mourey et al., 2005; Yancy et al., 2005), but efforts to understand and address these problems have been hindered by low levels of minority participation in health studies (Levkoff and Sanchez, 2003; Moreno-John et al., 2004). A review by Yancey et al. (2006) analyzed the factors that influence minority recruitment and retention in research studies. The findings revealed a lack of trust in inves-

tigators and the government, resulting from suspicions that participants would be mistreated for the benefit of scientists' careers and not their community's health. To address this issue, the involvement of researchers in the community has been shown to build trust and increase study participation. Community involvement may be achieved through the appointment of local outreach workers to communicate the potential benefits of research to the public and by the employment of minority investigators to serve as "cultural insiders." The identification and use of specific hubs of activity, such as places of worship, can also help build trust in research efforts and serve as places of recruitment (Yancey et al., 2006).

Another approach to increasing the involvement of underrepresented populations in research is the creation of community advisory boards that consistently meet to discuss a study's progress and any potential concerns by the public. This provides an external perspective and allows for participants to actively involve themselves in the study's ethical implementation (Manolio et al., 2012). According to the 2015 NIH survey, 71 percent of respondents felt that participants and researchers should be "equal partners" in the study, with a majority agreeing that participants should help decide what research is appropriate and what to do with study results (PMI Working Group, 2015).

Participant retention can be improved by taking the time to have a consistent follow up to personally engage participants and by creating materials that are culturally tailored (Yancey et al., 2006). Data collection centers that are easily accessible, particularly in rural areas, have demonstrated success in retaining participant involvement (Iredale et al., 2005). While the use of regularly timed incentives could be considered in communities that express a desire for them (Yancey et al., 2006), the belief that the participant is doing something beneficial for his or her future generations may be all the incentive that is needed.

For consortium models, it may be important for researchers to acknowledge the importance of local community engagement, since many ongoing cohort studies are invested in their own customized methods that have proven locally successful. If they are to be assimilated into a larger consortium, researchers may need to explore a balance between a centralized data collection system and the localized methods of specific sub-cohorts (Manolio et al., 2012).

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