ANNUAL REVIEWS

Annual Review of Genomics and Human Genetics

Early Lessons from the Implementation of Genomic Medicine Programs

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Annu. Rev. Genom. Hum. Genet. 2019. 20:389–411

First published as a Review in Advance on February 27, 2019

The *Annual Review of Genomics and Human Genetics* is online at genom.annualreviews.org

https://doi.org/10.1146/annurev-genom-083118-014924

Keywords

implementation science, learning health-care system, massively parallel sequencing, outcomes, precision medicine, precision health

Abstract

Massively parallel sequencing is emerging from research settings into clinical practice, helping the vision of precision medicine to become a reality. The most successful applications are using the tools of implementation science within the framework of the learning health-care system. This article examines the application of massively parallel sequencing to four clinical scenarios: pharmacogenomics, diagnostic testing, somatic testing for molecular tumor characterization, and population screening. For each application, it highlights an exemplar program to illustrate the enablers and challenges of implementation. International examples are also presented. These early lessons will allow other programs to account for these factors, helping to accelerate the implementation of precision medicine and health.

1. INTRODUCTION

Over the last decade, precision medicine has gone from a concept to clinical viability, albeit only in a few settings. The call by President Obama at the 2015 State of the Union address for a federally funded large-scale precision medicine initiative (15, 68) emphasizes the interest in this emerging care paradigm.

Medicine as currently practiced is empiric and dependent on the knowledge and experience of the individual provider, resulting in highly variable care with suboptimal outcomes. While much of this variability is driven by systematic issues within the care delivery system, some of it is due to the way evidence for interventions is currently generated. Interventions are tested against defined populations of individuals, and if the net benefit of the intervention is positive—that is, more individuals in a population respond than do not respond—and the adverse event rate is acceptably low, then the intervention may move into clinical practice. Providers will then apply the intervention to individual patients that share some characteristics with the study population and observe them for an empiric response. This is inefficient, leading to suboptimal treatment and risk of side effects, and impacts adherence to treatment.

Evidence is accumulating that genomic variants account for some of the variation in response to therapy. This realization has led to the concept of precision medicine. Several terms in this area have been used somewhat interchangeably, leading to confusion (see the sidebar titled What's in a Name?). In addition, precision medicine has been inappropriately conflated with genomic medicine, inaccurately implying that genomic information may be more important than other clinical information. However, an increasing number of examples demonstrate that having genomic information available to inform care can improve outcomes. While the focus of this review is on genomic medicine generated by massively parallel sequencing (MPS), it is important to understand that genomics is only one component needed to realize precision health.

WHAT'S IN A NAME?

The following terms are often used somewhat interchangeably but in fact have distinct meanings:

- **Genomic medicine:** As defined by the National Human Genome Research Institute (52), genomic medicine is "an emerging medical discipline that involves using genomic information about an individual as part of their clinical care (e.g., for diagnostic or therapeutic decision-making) and the health outcomes and policy implications of that clinical use."
- **Personalized medicine:** In a definition commonly attributed to Pauker & Kassirer (56), personalized medicine is "clinical decision-making such that the decisions made maximize the outcomes that the patient most cares about and minimizes those that the patient fears the most, on the basis of as much knowledge about the individual's state as is available" (41, p. 1). Three key points: (*a*) The focus is on outcomes of care; (*b*) the outcomes are patient defined (both positive and negative); and (*c*) the definition does not explicitly include genetics or genomics, so their value is not inappropriately emphasized.
- **Precision medicine:** As defined by Christensen et al. (13, p. 37), precision medicine is "the provision of care for diseases that can be precisely diagnosed, whose causes are understood, and which consequently can be treated with rules-based therapies that are predictably effective." This contrasts with the current empiric, trial-and-error approach.
- **Precision health:** Precision health encompasses the principles of precision medicine but extends them to include prevention as well as intervention.

1.1. Applications of Massively Parallel Sequencing

MPS is being proposed as an efficient approach for a diverse set of clinical scenarios because of its ability to query multiple genes and variants in a single assay. When more than two or three genes are relevant to the condition under study, using an MPS panel [or either exome sequencing (ES) or genome sequencing (GS)] is much more cost-effective than testing single genes sequentially. In this review, the discussion of genomic medicine using MPS focuses on four clinical settings: pharmacogenomic (PGx) testing, diagnostic testing, somatic testing, and population screening.

1.1.1. Pharmacogenomic testing. The pharmacogenome is the subset of the genome that codes for proteins involved in drug transport, metabolism, and response (including adverse events) (D.M. Roden, H.L. McLeod, M.V. Relling, M.S. Williams, G.A. Mensah, et al., manuscript in preparation). While some PGx information can be extracted from GS and ES data, the most effective PGx testing approach uses MPS panels constructed for this purpose. Panels such as PGRNseq (29) and a rapidly increasing number of commercially developed tests can capture information related to copy number variants and interrogate areas of the genome that are problematic for ES or GS, such as the human leukocyte antigen (HLA) region.

1.1.2. Diagnostic testing. Diagnostic testing can determine what is causing a specific set of signs, symptoms, or laboratory or imaging findings in a patient. Currently, this is the most clinically mature indication for MPS. MPS is used in situations where a clinical diagnosis is suspected but several genes can lead to the same phenotype (e.g., deafness) or when a specific clinical diagnosis is not evident but a genetic etiology is strongly suspected (e.g., multiple congenital anomalies that do not fit known genetic conditions). MPS-based approaches, such as gene panels and ES, have been used for a variety of clinical indications where the burden of genetic disease is high, including in critically ill newborns and for neurodevelopmental brain disorders (e.g., intellectual disability, autism, and seizures), multiple congenital anomalies, genetic syndromes, deafness, cardiomyopathy, and a host of other disorders (27). Evidence is emerging that supports the use of MPS-based approaches as a first-line test for several indications based on diagnostic yield, decreasing sequencing costs, and changes in medical management (58, 63).

1.1.3. Somatic testing. Genetic changes in specific tissue types can cause disease. The most common example is cancer, which at the level of the cell is a purely genetic disease. One of the most exciting developments in the treatment of cancer has been the identification of molecular signatures that can be targeted by specific therapeutic agents (50). This indication, now called precision oncology, has been used for several years. Medications like trastuzumab (Herceptin) or imatinib (Gleevec) were specifically designed for use in tumors that expressed specific molecular signatures: Her2/Neu in breast cancer and BCR/ABL in chronic myelogenous leukemia. Molecular tumor profiling using MPS technologies is being applied to direct therapy in cancers that have been traditionally resistant to therapy, such as non-small-cell lung cancer (NSCLC). Many genes and variants can drive oncogenesis in NSCLC. As with the genetic conditions discussed above, MPS-based assays are the most efficient way to profile tumors to guide therapeutic interventions. Although this approach is still in the early stages of use, it has demonstrated success in NSCLC (59) and other cancers (49) and has led to approval of molecularly targeted therapies (17). MPS tumor profiling usually provides information restricted to the tumor, but some approaches, such as paired ES for normal and tumor tissue, can yield information on germline genetic information that may be relevant to the patient.

1.1.4. Population screening. MPS can be applied to unselected populations of patients as a screening test to identify risk for genetic disease in the absence of signs or symptoms. At present, this screening is being conducted primarily in the research setting [e.g., ClinSeq (51) and MyCode (8)] and as part of some national efforts [e.g., in Estonia (42) and England (28)], but it is also starting to be used in clinical care and is emerging in direct-to-consumer MPS testing.

1.2. Implementation and the Learning Health-Care System

The other focus of this review is implementation. The Institute of Medicine (now the National Academy of Medicine) estimated that, because of the reliance on passive diffusion to move evidence into practice, it takes 17 years for interventions with evidence of effectiveness to become routinely used in medical care (47). This is unacceptable and has led to the development of the field of implementation science. Implementation science uses standardized and rigorous methods to evaluate approaches in order to move evidence into practice and evaluate the outcomes of the implementation in a systematic way. The outcomes are used to iteratively improve the program by accounting for factors that emerge in the implementation that were not accounted for in planning. This approach creates a so-called virtuous cycle that optimizes the implementation and provides the basis for sustainability. It also accounts for the impact of local contextual factors that can vary from site to site.

Out of this new discipline emerged the concept of the learning health-care system. In 2007, the Institute of Medicine (37) published the first workshop summary on learning health-care systems, which it defined as systems in which "science, informatics, incentives, and culture are aligned for continuous improvement and innovation, with best practices seamlessly embedded in the delivery process and new knowledge captured as an integral by-product of the delivery experience" (39, p. 1). This approach contains the components needed to synthesize complex and disparate information and present this information to the clinician and patient at the time of clinical decision-making in a reliable and reproducible fashion. Anticipating the emergence of genomics into practice, and recognizing the challenges identified by prior efforts, in 2015 the Institute of Medicine (38) published a workshop summary describing genomics-enabled learning health-care systems. While much of the focus was on electronic health records (EHRs) and data management, one speaker noted that "a health care system in which an infrastructure supports complete learning cycles that encompass both the analysis of data to produce results and the use of those results to develop changes in clinical practices is a system that will allow for optimal learning" (38, p. 19). A key concept of the learning health-care system is that there are no bright lines separating clinical care, quality improvement, and research. All these disciplines must be aligned and applied to optimize care to realize the learning health-care system.

Definition and measurement of outcomes are essential to understanding the impact of an intervention. Outcomes fall into several different categories (**Table 1**). The decision about which outcomes to capture for a given implementation depends on the nature of the intervention and should represent the perspective of the relevant stakeholders. Pragmatic decisions about the ease of capturing specific measures influence the choice of outcomes. Unfortunately, this has led to an overreliance on process outcomes that may have tenuous evidence for a relationship to health outcomes of interest. It has also resulted in more evidence about physician reactions to interventions as opposed to patient reactions, which is more relevant to patient-centered care.

2. LESSONS FROM GENOMIC MEDICINE IMPLEMENTATION

This section describes learning health-care system approaches to the implementation of genomic medicine. Each of the exemplar programs exhibits the principles of a learning health-care system

Table 1 Framework of outcomes for the clinical implementation of genomic medicine

Outcome type	Description	Example(s)
Process	The specific steps in a process that lead (either positively or negatively) to a particular health outcome	A lipid profile performed after return of a pathogenic variant in *LDLR*, a gene associated with familial hypercholesterolemia
Intermediate	A biomarker associated (either positively or negatively) with a particular health outcome	A low-density-lipoprotein cholesterol level at or below the target level of 100 mg/dl in response to interventions recommended based on the presence of a pathogenic variant in *LDLR*
Health	Change in the health of an individual, group of people, or population that is attributable to an intervention or series of interventions	A decrease in myocardial infarction or cardiac revascularization procedures in response to interventions recommended based on the presence of a pathogenic variant in *LDLR*
Cost	Standard costs associated with the interventions and health states experienced by the patient; can also include costs associated with patient-reported outcomes about health state and life disruption	Cost of sequencing Cost of genomics results delivery infrastructure Direct costs of care related to return of genomic information Utilization
Behavioral	Change in patient or provider behavior attributable to genomic information	Improved adherence to medication Modification of care based on condition-specific recommendations
Patient-reported	Report of the status of a patient's health condition, knowledge, or service outcomes that comes directly from the patient, without interpretation of the patient's response	Satisfaction with service Engagement with self-care Knowledge about gene and disease Access to recommended care Self-assessed well-being Family communication of genomic risk result and uptake of cascade testing

utilizing the tools of implementation science. While these are by no means the only programs taking this approach, the information available from publications and other sources supports analysis of the implementation, identifies lessons learned, and reports early outcomes from the program, enabling others considering the implementation of genomic medicine intervention to learn from these early adopters.

2.1. Pharmacogenomics

In many ways, PGx is the most mature application of MPS. This is due in no small part to extensive investments in projects and resources such as the Pharmacogenomics Research Network (PGRN; **https://www.pgrn.org**). Recognizing the need for a reliable resource to support PGx implementation, the PGRN created PharmGKB (**https://www.pharmgkb.org**), a publicly available online knowledge base responsible for the aggregation, curation, integration, and dissemination of knowledge regarding the impact of genomic variation on drug response. Of even more importance for clinical implementation was the need for evidence-based recommendations to inform the use of PGx information in practice. The Clinical Pharmacogenetics Implementation Consortium (CPIC; **https://cpicpgx.org**) provides guidelines that enable the application of PGx test results for drug choice and dosing. CPIC guidelines (14) are peer reviewed, publicly available, and periodically updated to reflect up-to-date knowledge. One important point about these guidelines is that they presume that the PGx information is already available—that is, they provide information not on when to order a PGx test, but rather on how to use the information from a test

to inform drug choice and dose. This illustrates a key question for the implementation of PGx: Should broad genomic testing be done prior to an indication for the testing (preemptive testing), or should selective testing be done at the time an indication arises (reactive testing)?

Prior to the advent of MPS, clinicians utilized reactive testing for the gene(s) and variants directly relevant to the drug being prescribed. While this approach had the advantage that it was clear how the test information would be used, the delay between when a test was ordered and when the result was available to inform the prescription delayed the therapeutic intervention and disrupted the usual clinical workflow. This proved to be one of several barriers to the implementation of PGx-informed prescribing. As MPS panels that tested for dozens of pharmacogenes became available, the concept of preemptive testing began to emerge. In this scenario, a patient is tested using such a panel (with or without a prescribing indication), and the information is stored and made available at the point of care when the clinician is prescribing a medication for which relevant information is available, much like an allergy or interaction alert. This minimizes the delay in prescribing and workflow disruption. This method proved to be feasible and was studied in several settings, as reported by Dunnenberger et al. (18) in 2015.

As with any novel intervention, barriers were identified to implementation. These included lack of guidance for the use of the information at the point of care, inability of the information technology infrastructure to store and present genomic information, lack of education of providers and patients about the usefulness of the data (coupled with a general lack of supporting evidence for use of PGx in care), and issues of cost and reimbursement. Strategies to overcome these barriers have allowed the programs to move from a research setting to clinical implementation in many cases.

2.1.1. The Mayo Clinic Center for Individualized Medicine pharmacogenomics program. The Mayo Clinic, a large academic medical center located in Rochester, Minnesota, initiated its PGx program in 2012. In 2017, Caraballo et al. (7) described the multidisciplinary model used at this clinic to implement PGx at the point of care. The description details extensive planning and preparation followed by implementation, evaluation, and iterative improvement, leading to a robust and sustainable program. The program leaders identified eight interrelated functional components that are briefly described below.

2.1.1.1. Institutional leadership support. Caraballo et al. (7) noted that, although pockets of utilization of PGx information were present in the system, the complexity of a large organization made dissemination challenging. To address this, institutional leadership was engaged to prioritize the implementation of PGx throughout the system. This facilitated coordination and provided resources necessary to support the implementation.

2.1.1.2. Governance. Given the complexity of the program, a governance structure was necessary to oversee its implementation and evaluation. The broad reach of PGx testing across multiple clinical settings necessitated a multidisciplinary governance structure. This structure included representatives from the areas of genomic medicine, primary care and relevant specialty services, pharmacy, laboratory, education, research, informatics (including information technology), and administration. A clear reporting structure was established to facilitate communication to system leadership and everyone affected by the implementation. The governance team was tasked with reviewing available evidence based on a diverse set of criteria used to prioritize which drug–gene pairs would be proposed for clinical implementation.

2.1.1.3. Clinical approval. Providers were engaged in the approval process to ensure that the drug–gene pairs proposed for implementation were relevant to current practice and the evidence was sufficient to support clinical use.

2.1.1.4. Laboratory results. Implementation is dependent on clearly defined values and terms. PGx results have been represented using an idiosyncratic naming convention (the star allele system) that worked well in basic science laboratories but was problematic in clinics. In addition, the clinical phenotypes inferred from genomic variants were fraught with multiple descriptors that were used inconsistently and proved to be confusing to clinicians. The PGx program invested significant effort to develop a standard representation of results and clinical descriptors to facilitate interpretation of the PGx information and allow electronic interfaces between the laboratory and clinical information systems, enabling just-in-time presentation of PGx information at the point of care. This representation also supported the development of embedded clinical decision support (CDS) systems in EHRs that provide additional support for providers to use the information appropriately (see the sidebar titled Clinical Decision Support). Efforts by CPIC have now standardized the clinical phenotype descriptors, reducing one implementation barrier (9). PGx variant representation does remain problematic, although ongoing work between PGRN, PharmGKB, and the Clinical Variant Resource (ClinVar; **https://www.ncbi.nlm.nih.gov/clinvar**) will hopefully lead to clinically robust standards that reduce the need for manual variant curation.

2.1.1.5. Pharmacogenomics education. Numerous studies have identified significant deficiencies in genomic literacy (33). Recognizing this gap, the PGx program developed a comprehensive educational program targeted at clinicians and pharmacists. This program included traditional educational approaches combined with just-in-time education embedded in provider and pharmacist workflows. End users preferred the latter approach.

2.1.1.6. Pharmacogenomics knowledge. A key component was a reliable source of vetted knowledge that could support the implementation. The CPIC guidelines (14) were identified as the primary source of peer-reviewed knowledge about drug–gene interactions. In situations where the guidelines were thought to be inconsistent with local knowledge and practice, the program engaged clinical experts to reconcile the knowledge before use in the clinic. The knowledge was formatted into narrative paragraphs, and translational tables were made available in EHRs, where they could be used by the CDS rules engine.

CLINICAL DECISION SUPPORT

CDS "provides clinicians, staff, patients, or other individuals with knowledge and person-specific information, intelligently filtered or presented at appropriate times, to enhance health and health care" (55, p. 141). There are three main approaches for the delivery of CDS:

- **Passive CDS:** Consists of nonmandatory resources available at the time of care, such as access to electronic resources through an EHR. This type of CDS requires that providers know they have a question.
- **Asynchronous CDS:** Presents information to the clinician outside of the clinical workflow, such as an inbox message at the beginning of the workday that lists preventive care interventions that are needed for the patients on the schedule. This type of CDS dramatically reduces the time involved to identify care gaps that need to be addressed and can provide clinicians with information that they might not otherwise know to look for.
- **Active CDS:** Presents information needed for a clinical decision at the time the decision is being made as part of the clinical workflow. Information is presented just-in-time at the point of care. Like asynchronous CDS, active CDS can provide clinicians with information that they might not otherwise know to look for.

2.1.1.7. Implementation of clinical decision support with electronic health records. The EHR ecosystem is essential for clinical implementation of CDS. The commercial EHR systems available when the Mayo Clinic started its program did not support PGx implementation, a situation that continues to the present day. This necessitated building and adapting functionality that was present in the systems to support the clinical workflow needed for synchronous and asynchronous provider notifications. To support different workflows, the program included both active and passive CDS (see the sidebar titled Clinical Decision Support).

2.1.1.8. Evaluation. An evaluation plan is essential to any PGx implementation. The outcomes to be measured should be defined at the outset, with provisions to modify them if unanticipated issues arise. For the PGx program, the primary outcome was the implementation and integrity of the program model. The defined components to be measured included adherence to the proposed model, implementation time (time between clinical approval and deployment), delay time (time between targeted implementation and EHR implementation), and number of unique providers and patients interacting with the interventions.

At the end of the study period, 21 PGx-CDS interventions were approved and 18 were implemented. The implementation and delay times were highly variable (ranges of 98–392 days and 0–148 days, respectively). While several factors influenced the variability, the two most important challenges involved clinician resistance to approval and technical issues related to formatting the results for the EHR, requiring significant customization. The reach of the PGx-CDS program was significant, with nearly 1,250 unique providers and 3,800 patients affected by an intervention, the most common of which was a pop-up alert. To date, the project has not published any results on the impact on patient outcomes.

2.1.2. The impact of pharmacogenomics implementation on outcomes: the Translational Pharmacogenetics Program Implementing Genomics in Practice experience. No publications have yet reported health outcomes from an implemented clinical PGx program. The Translational Pharmacogenetics Program of the PGRN collected pharmacogenetic implementation metrics from eight US health-care systems (43). The program collected outcomes in four domains: scientific, educational, financial, and informatics. No information was provided about patient outcomes. Subsequently, members of the Translational Pharmacogenetics Program along with other groups in the Implementing Genomics in Practice (IGNITE) network presented the results of a multisite pragmatic observational study examining outcomes from the use of *CYP2C19*-guided antiplatelet therapy after percutaneous coronary intervention (10). The study identified a significant difference in major adverse cardiovascular events, with a significantly higher event rate in patients with a *CYP2C19* loss-of-function allele treated with clopidogrel (a prodrug that must be enzymatically converted to the active drug by the gene product of *CYP2C19*) compared with those treated with alternative antiplatelet therapy not dependent on CYP2C19 (23.4 versus 8.7 events per 100 patient-years, adjusted hazard ratio of 2.26 with a range of 1.18–4.32, $p = 0.013$). Similar results were observed in a second set of patients who had percutaneous coronary intervention in the context of acute coronary syndrome (adjusted hazard ratio of 2.87 with a range of 1.35–6.09, $p = 0.013$). There was no difference in major adverse cardiovascular events between patients with no *CYP2C19* loss-of-function allele and those with a *CYP2C19* loss-of-function allele treated with alternative therapy. While this work was done in a research implementation, the real-world setting for the trial provides some of the first evidence supporting the potential for clinical PGx to improve health outcomes.

Another paper from this group comprehensively studied the implementation challenges of this drug–gene pair (19). This study is a good example of a learning health-care system approach to

implementation where information about outcomes and the contextual factors that affect implementation is collected and used to improve the program. Collecting data on implementation from 12 different institutions provides rich information that increases the utility for other would-be implementers and improves the generalizability of the results.

2.1.3. International efforts: Ubiquitous Pharmacogenomics. In Europe, the Dutch Pharmacogenetics Working Group has served in a similar role to CPIC in the United States. Despite accumulating evidence, PGx adoption has also been slow in Europe. In 2016, the Ubiquitous Pharmacogenomics program was announced (11). The project aims to implement preemptive PGx testing in clinical practice to develop evidence for the utility of this testing in Europe. Designed as a randomized clinical trial, the program intends to enroll 8,000 patients in seven European countries (the Netherlands, Spain, the United Kingdom, Italy, Austria, Greece, and Slovenia). The study proposes to use a composite endpoint that tracks outcomes that capture "specifically related clinical events (adverse events or events related to lack of efficacy)" (11, p. 206), scored using a numerical scale for outcomes ranging from changes with little impact on the patient's quality of life up to the most extreme outcome, death. Secondary outcomes will focus on measuring factors that affect the implementation in the diverse settings. The first secondary outcome is a report of the development and implementation of CDS to enable the return of PGx results in EHRs (6). The trial is planned for five years and will provide valuable information for the field.

2.2. Diagnostic Testing

Successful evaluation of children with suspected genetic disorders has been dependent on the development of new technologies that increase the likelihood of establishing an etiologic diagnosis. The introduction of MPS, particularly exome sequencing, has increased the diagnostic rate for children with diverse neurogenetic conditions, deafness, and vision loss from 20% to nearly 80%; other conditions, such as congenital disorders of hearing and vision, have even higher rates of diagnosis (3, 23, 30). In one study, early application of rapid-turnaround MPS resulted in a diagnosis in nearly three-fourths of acutely ill newborns, with most diagnoses having an impact on clinical management (61). MPS is being used for an increasing number of indications, including cardiomyopathy, renal disease, primary immunodeficiency, and neuromuscular disease.

No systematic studies have been conducted of MPS implementation in a clinical setting. The primary reason is that MPS is used in the context of genetic testing, a process that has been in place in the clinic for decades. The processes used to guide testing are institution specific, leading to high variability in application. Programs of the Newborn Sequencing in Genomic Medicine and Public Health Consortium are studying how to optimize implementation and systematically collecting outcomes to define the value of newborn sequencing (5). One of the programs has detailed the development and implementation of a rapid-turnaround MPS program for acutely ill neonates (60). This program, which was initiated in 2015, has implemented a care pathway that facilitates the early application of MPS sequencing to sick neonates meeting predefined criteria for inclusion. The standardized process optimizes sample collection and processing, sequencing, interpretation, and reporting. Outcomes of care are defined and collected. Iterative process improvements have decreased the time from sample collection to reporting from 50 hours to as few as 26 hours. A retrospective analysis of outcomes for 42 infants randomized to either standard of care or rapid-turnaround MPS demonstrated significant differences in diagnostic rate, changes in management, and outcomes in the latter cohort (20). Further study is needed to confirm these important early results.

2.2.1. The Undiagnosed Diseases Network. While the previous example is important, its approach to implementation was highly dependent on the local environment, which has benefited from significant investments in equipment, bioinformatics pipelines, and specialized personnel, limiting its generalizability to other sites. Another research program, the Undiagnosed Diseases Network (UDN; **https://undiagnosed.hms.harvard.edu**), provides a different example of lessons learned.

The UDN began as a National Institutes of Health intramural program called the Undiagnosed Diseases Program (24). This program proved to be valuable for patients with complex disorders who had not been successfully diagnosed despite extensive evaluation. This "clinic of last resort" utilized the resources of the National Institutes of Health Clinical Center and combined clinical care with the most advanced research methods to evaluate and treat patients accepted to the program (25). It demonstrated its success by establishing a diagnosis in 24% of patients evaluated. The challenge was that only 160 of the 1,191 patients referred underwent evaluation. This led to the funding of the UDN to see whether the success of the National Institutes of Health program could be replicated while providing access to more patients.

To standardize the evaluation of patients referred to the UDN, processes were developed, collected in a manual of operations, and implemented across the UDN sites. This required significant time and effort and necessitated communication of best practices and challenges from each site to assure robust implementation at each site. Local contextual factors were accounted for that provided some latitude for each site to make optimal use of its resources. This also provided opportunities for innovation at the site level, with local successes shared with the network to iteratively improve the evaluation of patients referred to the UDN.

One UDN site, the Brigham Genomic Medicine (BGM) program, recently described its implementation of the project (31). The BGM program studied different components of the evaluation workflow, which included case ascertainment and informed consent (as this is a research project), genomic sequencing and data analysis, causality of candidate genes, crowdsourcing and matchmaker analyses, and reporting evidence to referring clinicians, as described below.

2.2.1.1. Case ascertainment and informed consent. To ensure that the patients evaluated are the ones most likely to benefit, a set of criteria were developed to help providers determine whether they should refer a patient to the program. These criteria were shared with all clinical departments. All referred patients undergo a comprehensive medical review by BGM personnel and are presented to the program. All referred patients and their family members undergo informed consent for participating, which includes consent for data sharing and crowdsourcing analysis.

2.2.1.2. Genomic sequencing and data analysis. MPS analysis is performed in a Clinical Laboratory Improvement Amendments (CLIA)–certified laboratory so that any results can be used in clinical care. A standardized bioinformatics analytic pipeline is used that includes multiple approaches to reliably support the two overarching components of the pipeline: alignment and calling of sequence variants, and interpretation of the functional consequences of the identified sequence variants. The pipeline is optimized for Mendelian disease discovery using specific inheritance modes. Putative causal variants must fulfill three criteria: cosegregation of the disease consistent with the mode of inheritance, rare occurrence (minor allele frequency of $\leq$0.1% in relevant populations), and a predicted functional impact on the gene product.

2.2.1.3. Causality of candidate genes. The most critical function is to establish an evidence level for causality of the variant in the candidate gene above a threshold where it is appropriate to report clinically. This is accomplished through two complementary approaches: identifying

additional cases (ideally two or more) with a similar clinical presentation and a putative causal variant in the same gene, and empiric functional experiments. These approaches are consistent with the American College of Medical Genetics and Genomics and the Association for Molecular Pathology criteria for variant interpretation (57).

2.2.1.4. Crowdsourcing and matchmaker analyses. One of the most innovative aspects of the BGM program is a crowdsourcing portal that is available to all physicians, clinical staff, and research faculty at the institution. The Health Insurance Portability and Accountability Act of 1996 (HIPAA)–compliant portal allows collaborative case analysis. The value of this approach was demonstrated in the first 30 cases evaluated by the program in that 17 of the cases were solved using the crowdsourcing approach. The program also takes advantage of publicly available case-matching projects such as Matchmaker Exchange (**https://www.matchmakerexchange.org**), which played a role in one of the cases.

2.2.1.5. Reporting evidence to referring clinicians. For the program to be successful, diagnoses and recommendations for care must be effectively communicated to support condition-specific management. At present, the program is using traditional methods, including face-to-face genetic counseling sessions and comprehensive written reports.

At the time of the report, the BGM program had evaluated 244 families and performed MPS on 122. Of these 122, 30 cases have received a causal diagnosis, and 48 have candidate diagnoses that require additional confirmation. Systematic assessment of outcomes beyond the rate of diagnosis has not been reported, although anecdotally some diagnoses have led to changes in management.

The UDN has published a report on nearly two years of experience (62). In this time period, 1,519 patients were referred to the program, of which 601 were accepted for evaluation; 57% of pediatric-aged patients were accepted, compared with 28% of adults referred. A large plurality of cases had a predominantly neurologic phenotype (40%), followed by musculoskeletal, immunologic, gastrointestinal, and rheumatologic phenotypes. At the end of the evaluation period, 382 of the 601 patients had completed their evaluations, with an overall diagnostic rate of 35%—an extraordinary achievement, given the extensive prior workup of the referred patients. MPS led to a diagnosis in three-fourths of the cases. The paper included only limited information on outcomes; it noted that 21% of the diagnoses led to a recommended change in care, although these changes were not detailed.

The report also assessed the cost of the evaluation. Based on standard costing, patients referred to the program had an average cost of evaluation of US$198,651. The average cost of the UDN evaluation was US$15,116, or approximately 8% of the pre-referral total. For the patients receiving a diagnosis, the average pre-UDN cost was US$305,428, compared with US$18,903 for the UDN evaluation. While definitive conclusions cannot be made, this suggests that application of a systematic approach to evaluation earlier in the disease course could result in significant cost savings. This is an important finding, as the second and last phase of funding for the UDN has just begun. One of the goals of the next funding cycle is to develop a model of sustainability such that patients with complex undiagnosed diseases can continue to have access to comprehensive evaluation absent research funding.

2.2.2. International efforts: The UK 100,000 Genomes Project. The 100,000 Genomes Project (28), a partnership between Genomics England and NHS England, was initiated in 2013 to establish the use of whole-genome sequencing in the UK National Health Service and be a catalyst for adoption of this new technology. To this end, the project prioritized two use cases for the application of MPS, one of which is rare diseases in children. As with the UDN, standardized

processes were developed for key aspects of the project, including sample acquisition and sequencing, standardization of submitted clinical data, central automated analysis, standardized computational prediction tools and variant databases, local interpretation and clinical reporting, and access to genomic data for research (65). Analysis of the first cases referred to the project showed an overall diagnostic rate of 22%, with higher rates in neurogenetic conditions, such as intellectual disability. A second publication detailed the challenges encountered in implementing the project (4). These challenges fall into areas that are common to other genomic medicine implementations and include patient engagement, provider education, consent, and resources to support the program, such as a test registry. The authors recognized that implementation of this program will require a clinical transformation—a key concept with any significant proposed change in clinical practice. The program grouped the issues into two large categories: those associated with a failure to recognize progress in the field where present, and a resistance to change in roles. Educational efforts can help to address the first concern, but doing so also requires evidence that will be convincing to stakeholders, such as providers and administrators. Patients who will benefit from the new approaches can be important agents for change, a position endorsed by the 100,000 Genomes Project, which reinforced the need for robust patient engagement efforts. To address the second issue, the program undertook a comprehensive review of the roles of different stakeholders in the delivery of personalized medicine and used evidence to inform revisions of roles to support the most efficient and effective delivery of care.

2.3. Somatic Testing

One of the fastest-growing areas for MPS is somatic testing of tumors (49). Sequencing of tumors has provided insights into the molecular mechanisms that drive tumorigenesis and is beginning to transform the approach to treating some cancers, most notably NSCLC, which has historically been challenging to treat (59). Multiple targeted agents have been approved for use in NSCLC based on the molecular signature of the tumor, and best practice guidelines support sequencing of these tumors (59). It is anticipated that use of sequencing will be extended to more types of cancer and may become a standard of care as more information accumulates about the impact of molecularly targeted cancer therapy.

Outcomes of molecularly targeted cancer therapies are being reported. In their review article, Morash et al. (46) summarized the results of several outcome studies. They indicated that the preliminary results are promising but also described several limitations. For example, they noted that none of the studies used a randomized controlled trial (RCT) design, although they also noted that application of RCT to precision oncology is challenging: Since MPS can identify so many different molecular targets, it is difficult to accrue enough patients across MPS subtypes to power an RCT for each subtype. Another issue is that only a minority of cancers have targetable variants based on current sequencing approaches and available medications. The Genomics Evidence Neoplasia Information Exchange (GENIE), an international data-sharing consortium, currently estimates that 30% of tumors across several cancer types have a targetable variant (1), although this percentage is expected to increase.

The authors of the GENIE study (1) also identified barriers to the implementation of molecularly targeted cancer therapy. These are similar to barriers to other precision medicine interventions and include physician and patient readiness, patient access to these advanced therapies, cost, and reimbursement issues. While not specifically mentioned, the technical issues of representing the information in EHRs is undoubtedly relevant.

While these barriers are challenging, in some ways oncology practice has already undergone a transformation to more protocolized care to reduce unexplained clinical variation and improve

outcomes. ProvenCare is an approach developed at Geisinger to take evidence-based care guidelines and best practices and convert them into executable protocols that can be tested and refined for optimization. These protocols are then implemented with the full support of the EHRs and associated data sources coupled with dashboards and other metrics to track outcomes and identify process failures that can be quickly remedied. ProvenCare demonstrates that linking several improvement concepts (evidence-based guidelines, data feedback, and reliability science) in a single design model can effectively reduce unwarranted variation in care delivery. The true value of these protocols is that they can be implemented by other systems with modest site-specific customization, yielding results similar to those seen at Geisinger. The best example of the potential of the ProvenCare approach in precision medicine is the multi-institutional lung cancer implementation under the auspices of the American College of Surgeons Commission on Cancer (40). In this project, six sites (including Geisinger) initially convened with the goal of eliminating unwarranted variation in the delivery of evidence-based care to patients diagnosed with NSCLC. The pilot was successful, with 90% of the 38 elements of care followed by the initial six pilot sites for each patient entered into the study. Another six sites were later added to the program. The sites include both traditional academic medical centers and community hospitals, validating the generalizability of the model. While the initial project did not include molecularly targeted therapies for NSCLC, these therapies are now being added to the care pathway. If successful, this program would represent the first multisite precision oncology intervention for a single cancer.

2.3.1. Intermountain Healthcare's precision cancer genomics program. Intermountain Healthcare established its precision cancer genomics program in one region of its service area (the Dixie region of southwest Utah) in 2013. The program has now expanded to encompass all Intermountain Healthcare regions and is offered to 1,000 patients a year. The program developed a systematic approach to the evaluation of patients with recurrent or metastatic solid tumors who failed first-line therapies based on the National Comprehensive Cancer Network guidelines. This approach included molecular characterization of the tumors to identify somatic mutations that were deemed actionable (defined as mutations for which there was validation in the peer-reviewed literature and for which a targeted therapy was available). The program created an infrastructure that included a molecular tumor board to evaluate the use of targeted therapy. It also engaged with stakeholders at the system level, including representatives from the provider-owned insurer as well as other payers to address the potential reimbursement issues for molecularly targeted therapies. The leadership also defined outcomes that would be collected for patients treated through the program and created a system to collect and analyze those outcomes.

2.3.1.1. Impact of the program. In 2017, the program published its first outcome paper, a retrospective evaluation of the impact of molecularly targeted therapies on progression-free survival and health-care costs (35). The authors used a matched cohort study of 72 patients with metastatic cancer of different types. Of these 72 patients, 36 were treated according to the precision oncology protocol, with genomic testing and use of targeted therapy based on the test results, and the results were compared with those of 36 historical controls matched for sex, age, histologic diagnosis, and therapies prior to the time point where sequencing would be considered. Progression-free survival significantly increased in the precision oncology cohort (22.9 weeks for those receiving the intervention compared with 12.0 weeks for the controls; $p = 0.002$, hazard ratio = 0.47, with a 95% confidence interval of 0.29–0.75). A subset of patients ($n = 44$) were managed entirely within the Intermountain Healthcare system, so the complete costs of medical care could be assessed. The cost of care per week was US$4,665 in the intervention group and US$5,000 in the controls, a nonsignificant difference. The authors acknowledged the potential for bias in a retrospective

study of this nature, but noted that matching for previous lines of treatment received before study enrollment mitigated (but did not eliminate) the risk.

This study was followed by a second retrospective study to examine a broader range of outcomes, including impact beyond the traditionally defined progression-free survival window and average total health-care costs and utilization over the entire observation period (34). A cohort of 44 patients was identified, with 22 patients in the intervention group matched with 22 historical controls using the same criteria. In this analysis, the patients treated under the precision oncology protocol had a median overall survival of 51.7 weeks compared with 25.8 weeks in the control group ($p = 0.008$). The average cost per week was US$2,720 for the precision oncology patients and US$3,453 for the controls ($p = 0.036$). Given the small size of the study, the authors performed an unplanned post hoc cost analysis for the overall population of late-stage cancer patients that were covered under the provider-owned health plan. Of a total population of 1,814 patients who met the inclusion criteria, 93 had received treatment using the precision oncology protocol. In this analysis, the cost of care for the last three months of life was 6.9% lower in the precision oncology group compared with those who did not receive a precision oncology intervention. Most of the cost reduction was attributed to a marked reduction in inpatient hospitalization, which more than offset the increased pharmacy costs associated with the use of expensive targeted therapies. This finding also has a significant implication for patient-centered care in that most patients with a terminal illness prefer not to be hospitalized. It is important to note that, while the average per-week cost of care was lower, the total cost of care for the precision oncology patients was higher, given that their survival period was on average twice as long as that of the controls. When this information was presented to health plan representatives, they noted that the increased survival was a more important outcome than the increased total cost of care from their perspective.

2.3.1.2. Dissemination and implementation. In the second retrospective study (34), the authors noted that a major weakness of the study was that it was conducted in a single institution, and therefore the generalizability of the approach was untested. To address this issue, the precision oncology team at Intermountain Healthcare worked with two other systems: Providence St. Joseph Health and the Stanford Cancer Institute. Intermountain Healthcare is an integrated health-care delivery system, which means that providers, hospitals and other care centers, and a payer are all under the same corporate umbrella, providing an opportunity to align incentives and promote innovative approaches to care. Providence St. Joseph Health is a community care center based in Renton, Washington. It is a large not-for-profit system with 50 hospitals and more than 800 clinics providing services across seven western states. The Stanford Cancer Institute is part of Stanford Medicine, a traditional academic medical center. As such, it has a research mission that complements its patient care mission. As a National Cancer Institute–designated Comprehensive Cancer Center, in addition to caring for cancer patients, it oversees a portfolio of cancer-related research ranging from basic science to population-health investigations.

These three organizations represent significant diversity in mission and approach to care, and all three have implemented precision oncology programs. In 2018, Nadauld et al. (48) reviewed the implementation of these programs to characterize lessons learned that could facilitate the implementation of precision oncology care more broadly. Key barriers to implementation experienced by all three organizations included the need for new informatics tools; analysis and modification of clinical workflows to support the new care paradigm; access to the necessary genomic testing; the need to capture, analyze, and interpret molecular data in a time frame that was relevant to clinical decision-making; collection and analysis of molecular, clinical, and cost outcomes; evolving knowledge about the impact of molecular alterations in the tumor; access to and approval of the use of targeted therapies; and inconsistent payer reimbursement policies to support these

interventions. The creation of a joint molecular tumor board across the three organizations was a key enabler to address several of these barriers. It is hoped that identifying these issues can also generate a policy agenda to address issues related to off-label use of targeted therapies, improve access to these therapies, and reduce the attendant reimbursement issues.

The Intermountain Healthcare program is so innovative that it was the subject of a Harvard Business School case study (32). The case study examined the program's organization and implementation, the executive support needed to implement it, how outcomes were defined and measured, and the integration of the program within the larger health-care system.

2.3.2. International efforts: The UK 100,000 Genomes Project and NHS England. The other area of focus of the UK 100,000 Genomes Project is oncology, which NHS England had prioritized in its *Five Year Forward View* document (53). Genomics-led personalization of treatment, including cancer treatment, was initially described in 2016 (54), and significant progress has been made since then (66). While the program has yet to be fully implemented, initial reports based on several hundred tumor analyses returned to clinicians estimate that 65% of the tumors have variants in genes that are potentially amenable to targeted therapeutic approaches (36). A significant investment in infrastructure is under way, and studies are needed to determine how such targeted therapies can be implemented. This approach will require a transformation of current routine oncologic care that incorporates a variety of issues, including consent, sample collection and handling, integration of clinical genetics expertise, and creation of an informatics infrastructure to support the collection and use of the disparate data elements (36). NHS England recognizes the need to share data and learn from others who have implemented precision oncology and call for the establishment of international partnerships to facilitate the implementation globally.

Although this is outside the scope of this section, it is important to note that the UK 100,000 Genomes Project is planning to analyze the genomic sequences generated to identify individuals with germline pathogenic variants in known cancer predisposition genes (e.g., *BRCA1/2* and mismatch repair genes associated with Lynch syndrome) (4). This population screening approach, when implemented, fits within the final section of this review, on population screening.

2.4. Population Screening

Use of MPS for population screening has not been implemented as a clinical service, which is appropriate because there are several unanswered questions about its application in this setting. For example, what gene–disease associations should be screened for? Should a population screening program include some intervention that alters management of a condition, or is information alone sufficient? Given that the low prior probability of disease raises the risk for false positive interpretations, how conservative should variant interpretation be? What is the evidence that supports the idea that this approach will improve health outcomes? What is the risk that erroneous interpretation will result in inappropriate care? And how will analysis be updated as new knowledge accrues? MPS implementations in clinical research settings will enable studies that explore these and other questions to determine whether MPS can be deployed for population screening; if the evidence supports such use, then these early programs can provide key insights to inform successful implementation.

2.4.1. Geisinger's MyCode® Community Health Initiative. Geisinger is a rural, integrated health-care delivery system in central Pennsylvania and southern New Jersey that serves approximately 4.2 million residents, with approximately 1.5 million unique patient visits annually. Approximately one-third of Geisinger patients are insured by the provider-owned Geisinger

Health Plan, creating a sweet spot that enables Geisinger to pilot innovations in care delivery (64). The MyCode® Community Health Initiative (hereafter referred to as MyCode; **https://www.geisinger.org/mycode**) began as a biorepository with linkage to EHRs in 2007 (8). In 2014, Geisinger entered into a partnership with Regeneron Pharmaceuticals and the Regeneron Genetics Center that would generate exome sequences, high-density genotypes, and HLA typing for all consented participants (16). The primary purpose of the collaboration was drug discovery; however, the potential value of the exome sequences for clinical care was recognized, and Geisinger negotiated for full and unrestricted clinical use of the exome data. The genomic data are generated by Regeneron in a research setting, so any result to be returned must undergo confirmation in a CLIA-certified clinical laboratory. MyCode participants are enrolled under a broad, opt-in consent that supports health-related research and allows for the recontact of participants and reporting of results that are deemed clinically relevant, with placement of results in the EHRs. This provides an opportunity to benefit participants, something that was valued by Geisinger patients in the extensive community consultation used to design and continuously improve the program (21). Oversight is provided by the Geisinger Institutional Review Board and the MyCode Governing Board, with input from other stakeholders, including participant, youth, and clinician advisory boards; a genomic council consisting of all Geisinger genetic providers and faculty; and external ethics and scientific advisory boards. This ongoing commitment to involve the broad community both within and outside Geisinger is key to maintaining trust and provides opportunities to adapt the initiative to the changing needs of the community (67).

Figure 1 shows the high-level processes needed to take the data from the research sequences through confirmation, return of results, and measurement of outcomes attributable to the return of results. The implementation of these processes utilizes the principles of the learning health-care system (37) and was described in detail in a recent article on implementation of precision medicine in a learning health-care system (70). Consenting and sample collection are not discussed here, as

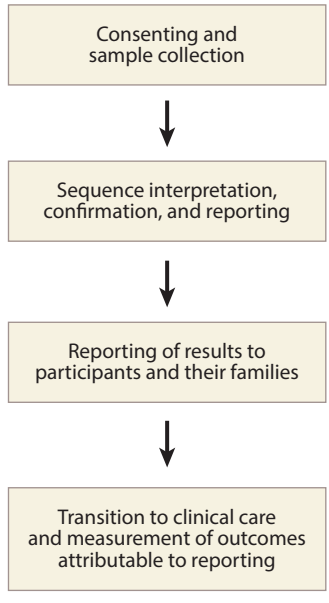

Figure 1

Overview of the processes for the Geisinger MyCode Community Health Initiative.

these are research processes that have limited relevance to clinical care. Key elements for each of the remaining processes include the following:

- Sequence interpretation, confirmation, and reporting entails performing bioinformatic analysis of the DNA sequence to identify high-confidence, likely, or known pathogenic variants; obtaining clinical confirmation of putative pathogenic variants in a CLIA-certified laboratory; receiving the report from the laboratory with placement in the EHR; notifying the participant's primary care provider; and depositing all confirmed variants in ClinVar.
- Reporting of results to participants and their families entails supporting primary care providers with educational materials and resources within the EHR relevant to the result being reported; contacting the participant with results using the patient portal, phone calls, and/or letters (a certified letter is used to close the loop if the participant cannot otherwise be contacted); supporting participant choice to follow up with their primary care provider or specialist provider and/or to have a visit with a member of the Genomic Screening and Counseling Program; and providing support for participants to give results to at-risk family members to facilitate cascade testing. Since this is a research program, a process is in place to make sure that costs related to the confirmation and initial results reporting are paid for by the Genomic Screening and Counseling Program and not the patient.
- Transition to clinical care and measurement of outcomes attributable to reporting entail creating a network of specialists and condition-specific clinics with expertise in disorders relevant to the genomic result; providing care coordination and navigation services to participants to help them navigate the system to get recommended care; developing systems to capture outcomes relevant to the conditions identified by sequencing and attributable to the return of results; and extending outcomes to include patient-reported outcomes.

Review of metrics associated with the reporting process combined with input from the advisory committees allows the identification of opportunities for process improvement followed by the development and implementation of these improvements.

MyCode currently has more than 227,000 consented participants, and exome sequencing has been completed on more than 92,000. Geisinger began providing genomic counseling and reporting actionable genomic findings to patients in 2016. It was initially estimated that 3.5% of participants would have a variant eligible for return (16). With refinements to the bioinformatics pipeline and curation, this estimate has been lowered to approximately 2%. As of December 2018, 1,050 results have been reported to 1,046 MyCode patient participants (4 participants had 2 reportable findings) (26).

Outcomes from the return of results are under study and are beginning to show the potential value of the program. Systematic analysis is needed to prove the value proposition on a wide scale. Manickam et al. (44) recently reported the results of an analysis of 267 MyCode participants clinically confirmed to carry a pathogenic or likely pathogenic variant in *BRCA1* or *BRCA2*. Participant medical records were reviewed to identify prior clinical testing for disease-associated variants in *BRCA1/2*, evidence of a personal history of disease consistent with *BRCA1/2*-associated hereditary breast and ovarian cancer (HBOC), and assessment of family history of HBOC, including comparison with guidelines for clinical testing. The study confirmed increased risk for breast and ovarian cancer in carriers compared with MyCode participants without a variant. The authors identified significant opportunities to close care gaps. They noted that fewer than half of participants identified as carriers met personal or family history criteria that would lead to a recommendation for clinical testing for *BRCA1/2*, confirming that the current testing criteria are not sensitive enough to identify individuals at risk. Of the participants who had sufficient clinical information to allow the application of testing guidelines and met criteria for clinical testing, only half had actually

received testing, which represents a failure of current care delivery to identify and test patients at risk for HBOC. The paper concludes, "These findings suggest that genomic screening may identify *BRCA1/2*-associated cancer risk that might otherwise remain undetected within health care systems and may provide opportunities to reduce morbidity and mortality in patients" (44, p. 2).

Another important issue is determining whether patients will use the results to change health behaviors and follow condition-specific recommended care. Studies are under way examining the Centers for Disease Control and Prevention's Office of Public Health Genomics tier 1 genomic applications with implications for public health (HBOC, Lynch syndrome, and familial hypercholesterolemia) (12). Preliminary analysis demonstrates significant health behavior changes attributable to the result (A.H. Buchanan, A.C. Sturm, M.L.B. Schwartz, M.S. Williams, D.H. Ledbetter, et al., manuscript in preparation). Of relevance to HBOC, surveillance recommended based on the result identified eight new cancer diagnoses following disclosure (three breast cancers, including one bilateral ductal carcinoma in situ; three prostate cancers; one fallopian tube carcinoma; and one carcinoma of the ampulla of Vater, all of which were stage IIB or earlier) (A.H. Buchanan, A.C. Sturm, M.L.B. Schwartz, M.S. Williams, D.H. Ledbetter, et al., manuscript in preparation). Analyses of this data set, including cost analysis and economic modeling, are under way.

2.4.2. International efforts: the Estonian Biobank of the Estonian Genome Center. In 2000, the Estonian Genome Foundation worked with the Estonian government to create the Estonian Genome Project. This partnership promoted legislative changes and encouraged government support to implement the project (45). While the initial goal was to collect biospecimens and health data on 70% of Estonia's population, financial constraints and reorganization have transitioned the project to the University of Tartu and reduced enrollment to just over 52,000 Estonians to date. The project collects questionnaire data on health (e.g., diet, lifestyle, and clinical diagnoses), standard health examinations, and genomic information from participants. Exome or genome sequences have been obtained from 52,274 participants (2).

The project recently published its first results, which focused on familial hypercholesterolemia (2). In this study, 4,776 of the sequenced participants had their sequences analyzed to identify pathogenic variants in one of three genes associated with familial hypercholesterolemia (*LDLR*, *APOB*, and *PCSK9*), and 27 variant carriers were identified. Through identification of these individuals, 60 at-risk relatives were tested for the familial variant, with an additional 20 carriers identified. Genetic counseling and clinical management were provided to all carriers, and 51% of carriers were reclassified from a nonspecific lipid disorder. Only three participants had previously been diagnosed with familial hypercholesterolemia. Statin use was confirmed in fewer than 50% of the carrier participants and relatives, representing an opportunity for improvement. Image-based phenotyping was provided (carotid ultrasound and computed tomography for coronary artery calcification), which identified 20 patients with evidence of subclinical atherosclerotic cardiovascular disease. For more than half of the participants, either statin therapy was initiated or the dose was increased. This study demonstrates that precision medicine can be implemented in the setting of a national health-care system.

3. CONCLUSIONS

Genomic medicine is emerging from the research setting into clinical care. Evidence is accumulating to support the value of using genomics in conjunction with other personal and clinical data to realize the vision of precision medicine. The experience of early adopters has identified important lessons that can be used to inform subsequent implementations. It is important for implementers to share lessons learned, ideally using frameworks from implementation science (22), to

allow more rapid dissemination of successful approaches. Agreement on standardized outcomes relevant to genomic medicine is also critical to rapid learning and evidence development (69). Incorporating these lessons will accelerate the appropriate application of genomic medicine to improve patient care.

SUMMARY POINTS

1. Genomic medicine is emerging into clinical practice in the United States and internationally.
2. Current implementations are mostly institution or country specific and have therefore emphasized local solutions, with less attention paid to generalizability.
3. Successful implementation of genomic medicine requires support from organizational leadership but is facilitated by substantive engagement with relevant stakeholders to inform key aspects of the program and enhance acceptability.
4. Engagement with patients and families to understand their perspective on the use of genomic information to guide care is essential but has been underutilized, particularly to understand how to increase the uptake of testing at-risk relatives of an affected individual (cascade testing).
5. The current technology used in electronic health records (EHRs) and laboratory information systems does not support the incorporation of genomic information as structured, computable data, limiting the ability to create decision support systems that can aid providers in appropriate use of the information.
6. The implementation of genomic medicine represents a cultural transformation. Successful implementation must account for the cultural change in the health-care delivery system, not just the evidence of the information's value. Application of implementation science frameworks to the implementation of genomic medicine will identify these issues and generate best practices that can accelerate the dissemination across systems.

FUTURE ISSUES

1. EHR systems currently in use do not adequately support the use of genomic information in clinical care. Systems to support the use of genomic medicine, including clinical decision support, need to be developed and deployed either within the EHRs or in applications that can seamlessly interact with EHRs through application interfaces.
2. Outcomes attributable to the implementation of genomic medicine must be systematically collected and analyzed. It will be important to standardize the outcomes to be collected across all groups implementing genomic medicine to accelerate the evidence generation.
3. Data sharing to aggregate genomic knowledge and combine evidence is essential. Some examples exist for gene and variant knowledge (e.g., ClinVar and ClinGen), and there are examples of outcome definition and collection from National Human Genome Research Institute–funded projects, such as the Electronic Medical Records and Genomics

(eMERGE) network, the Clinical Sequencing Evidence-Generating Research (CSER) consortium, and the Implementing Genomics in Practice (IGNITE) network.

4. Implementation science frameworks must be used to collect information about the barriers and facilitators to the use of genomic medicine in the clinic. Information collected across multiple sites with diverse populations and settings can yield a complete set of issues that can be synthesized into an implementation guide that can reduce the burden on subsequent systems wanting to incorporate genomic medicine into care.
5. Diverse stakeholders, including patients, families, providers, administrators, payers, employers, and policy makers, must be engaged in order to understand the different perspectives on the value proposition for genomic medicine. The results can then inform data collection to address the questions of most importance to stakeholders.

DISCLOSURE STATEMENT

The author is an employee of Geisinger, which has an ongoing partnership with Regeneron Pharmaceuticals and the Regeneron Genetics Center, as described in the article. Neither the author nor the Geisinger clinical implementation project receives funding from Regeneron.

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