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Patient-Centered Precision Health In A Learning Health Care System: Geisinger's Genomic Medicine Experience

ABSTRACT Health care delivery is increasingly influenced by the emerging concepts of precision health and the learning health care system. Although not synonymous with precision health, genomics is a key enabler of individualized care. Delivering patient-centered, genomics-informed care based on individual-level data in the current national landscape of health care delivery is a daunting challenge. Problems to overcome include data generation, analysis, storage, and transfer; knowledge management and representation for patients and providers at the point of care; process management; and outcomes definition, collection, and analysis. Development, testing, and implementation of a genomics-informed program requires multidisciplinary collaboration and building the concepts of precision health into a multilevel implementation framework. Using the principles of a learning health care system provides a promising solution. This article describes the implementation of population-based genomic medicine in an integrated learning health care system—a working example of a precision health program.

Precision medicine is evolving from a concept to clinical viability, albeit in limited settings. In his 2015 State of the Union address, President Barack Obama called for a federally funded, large-scale precision medicine initiative, heightening interest in this idea.[1,2]

Medicine as currently practiced is empirical, inadequately grounded in evidence, and dependent on the knowledge and experience of individual providers, which results in variable care with suboptimal outcomes. Clay Christensen and coauthors define *precision medicine* as "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."[3]

Although some conflate genomic medicine with precision medicine or, as we prefer, precision health (as it encompasses both wellness and disease), genomic data must be combined with data from other sources (for example, clinical, environmental, and social) to inform precision care. The formulation that best captures what is needed to attain precision health is attributed to Stephen Pauker and Jerome Kassirer: 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.[4] This definition captures three key points: a focus on outcomes, the central role of patients in defining outcomes (positive or negative), and

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"knowledge about the individual's state" (which implicitly includes "genetic" and "genomic" information).

Health care systems as traditionally configured are not designed or equipped to deliver precision health to patients. In 2010 the Institute of Medicine (IOM) published *Value in Health Care*, the first of nineteen reports to date on learning health care systems. In its introduction to the series, the institute defined these systems as those 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."[5]

Prior IOM reports had not addressed genomic or precision medicine, so in 2015 the IOM published a workshop summary describing genomics-enabled learning health care systems[6] and emphasized the need for learning cycles that analyze data and use the analytic results to change clinical practice. Genomics-informed precision health is emerging in clinical practice, mostly in the setting of clinically relevant and informed research (exhibit 1).

This article focuses on high-level issues of relevance to any organization contemplating a precision health program. As a case study, it describes the initial phases of implementation of a large-scale population-based precision health initiative within the setting of a learning health care system.

The Setting

Geisinger is an integrated health care delivery system in densely rural (as designated by Medicare) central Pennsylvania and in southern New Jersey. Geisinger serves approximately 4.2 million residents, with about 1.5 million unique patient visits annually. About one-third of Geisinger patients are insured by the provider-owned Geisinger Health Plan. This creates a "sweet spot" that enables Geisinger to pilot innovations in care delivery.[7(p xix)]

CLINICAL CARE REENGINEERING AND QUALITY IMPROVEMENT Geisinger has over ten years of experience in creating evidence-based care pathways to reduce unexplained clinical variation, resulting in high-quality care at a lower cost and optimizing value to the patient, health system, and payer.[7,8] The pathways are implemented with the support of the electronic health record (EHR) system and associated data sources, coupled with processes to track outcomes. Patient engagement is an essential component of precision health and learning health care systems and must be included in the reengineering process to a greater degree than has occurred previously. This approach demonstrates that linking several improvement concepts (for example, evidence-based guidelines, data feedback, reliability science, and patient-centered care) in a single design model can reduce unwarranted variation in care delivery to reduce cost, optimize outcomes from the patient's perspective, and provide the foundation for continual improvement. Geisinger has facilitated the generalizability of locally developed standardized care pathways by converting them to condition-specific care protocols coupled with consultative services, a process termed ProvenCare.[7,8]

BUILDING A LEARNING HEALTH CARE SYSTEM Geisinger has committed to becoming a learning health care system, a goal facilitated by its organization as an integrated system in which all employees and units—including researchers, providers, and a payer—are part of the overall success of the enterprise. A multidisciplinary

EXHIBIT 1

Selected US programs that are implementing the use of genomic information in the health care setting

Program	Genomic information returned	Approximate number of patients
eMERGE phase 3[a]	Pathogenic and likely pathogenic germline variants in actionable genes, pharmacogenomics	25,000
IGNITE	Family history, pharmacogenomics, selected pathogenic germline variants, polygenic risk scores	—[b]
St. Jude Children's Research Hospital	Pharmacogenomics	All patients admitted for treatment (about 7,500 annually)
Inova Health System Translational Medicine Institute	Pharmacogenomics, pathogenic variants related to selected clinical indications	5,000
Geisinger MyCode® Community Health Initiative	Pathogenic and likely pathogenic germline variants in actionable genes, pharmacogenomics	92,000 to date

SOURCE Authors' analysis. **NOTE** IGNITE is Implementing Genomics in Practice. [a]Geisinger is a member of the Electronic Medical Records and Genomics (eMERGE) network. [b]Not publicly available.

working group consisting of representatives of key organizational functions, including research, clinical innovation, and bioethics, meets regularly to identify current assets and gaps that need to be filled to attain this goal.

Four phases have been defined to foster the development of a learning health care system. These are in the process of being implemented. Phase 1 involves developing criteria for identifying, evaluating, and tracking "local learning health care initiatives"—existing Geisinger practice areas that have already adopted at least some aspects of the learning health care system model. Phase 2 consists of identifying instances in which an initiative was successfully expanded into adjacent practice areas, identifying factors that enabled that spread, and leveraging those factors by deliberately linking initiatives to one another to enhance collaboration and replication. Phase 3 involves establishing an enabling core of providers who are empowered and incentivized to lead learning, experimentation, and innovation efforts and provide a model for others to follow. Phase 4 consists of developing conceptual and business models that, drawing on lessons learned in phases 1–3, will inform efforts to further advance and oversee a system-wide learning health care system culture.

Enabling Factors For Implementing Precision Health

Research—as part of the innovation cycle integral to learning health care systems—has been an essential part of Geisinger's mission since its beginning. The theme of the Geisinger research strategic plan is personalized health care research, with an emphasis on developing and testing innovative approaches that will enable the identification of patients' unique influences (environmental, clinical, social, and genetic) so that each patient receives the right care at the right time in the right way, to optimize quality and achieve the outcomes of importance to that patient.

With this goal in mind, senior leadership began to discuss the concept of a genomics core in the early 2000s[9] and led to the launch of the MyCode® biorepository in 2007.[10] From its inception, the biorepository used opt-in consent, allowing participants to contribute biospecimens linked to their EHR data that were initially used for discovery research. The potential of the MyCode biorepository as a first step in a precision health project was recognized in the 2010 revision of the research strategic plan.

Recognizing that research results from the MyCode initiative were of translational and clinical value, Geisinger established several institutes designed to span and integrate research and clinical care using the learning health care system model. They included the Obesity Institute, the Genomic Medicine Institute, and the Autism and Developmental Medicine Institute. To enable this integrative mission, each Geisinger institute is actively engaged with clinical care departments, clinical innovations, informatics, and the broader research enterprise.

As of January 2018, over 180,000 Geisinger patients had consented to participate in what is now called the MyCode Community Health Initiative.[10,11] Of the patients approached, 85–90 percent consent to participate. Ongoing analysis of the reasons patients decline participation has not identified any predictive factors. MyCode participants are slightly older and more likely to be female, have a higher body mass index, and are less diverse in terms of race/ethnicity, compared to Geisinger patients on average.[10] Participants have a median of fourteen years of EHR data.

In 2014 the MyCode initiative began to conduct whole exome sequencing and genotyping on collected samples, as part of a collaboration with Regeneron Pharmaceuticals and the Regeneron Genetics Center.[12] Whole exome sequencing analyzes genes that code for proteins and associated gene regulatory areas—about 1–2 percent of the whole genome containing the most clinically relevant information. To date, nearly 93,000 exome sequences have been completed.[11] Although these data are intended to support discovery research, Geisinger has unrestricted use of the data for clinical care. MyCode participants are now 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 EHR. This provides an opportunity to benefit participants, something that was valued by Geisinger patients in the extensive community consultation used to design the program and continuously improve it.[13]

Oversight is provided by Geisinger's Institutional Review Board and the MyCode Governing Board, with input from other stakeholders that include participant, youth, and clinician advisory boards; a genomic council consisting of all Geisinger genetic providers (medical and laboratory geneticists, and genetic counselors) and faculty members; and external ethics and scientific advisory boards. This ongoing commitment to involving the broad community both within and outside Geisinger is key to maintaining trust, and it provides opportunities to adapt the initiative to the changing needs of the community.[14] The partnership with patients, participants, and other stakeholders represented in

the advisory boards facilitates the alignment of science, incentives, and culture—keys to realizing a learning health care system—and reduces the risk of failure due to poor communication. An approach involving input from diverse stakeholders, informed by the patient's perspective, is essential for any organization seeking to implement precision health, as adjusting specific processes to the local environment is needed to maximize the likelihood of success.

Any new initiative of this magnitude and breadth requires significant resources. The costs of the MyCode initiative have been met through a combination of institutional investments and funds from Geisinger's partnership with Regeneron Pharmaceuticals, philanthropy, grants, and other sources. The MyCode program was designed to inform the implementation of genomics in clinical care at the scientific and process levels, as outlined in this article. While the initial stages of the program were not designed to enable cost-benefit analyses, this is an important focus of ongoing work.

Initial Implementation Of A Genomic Medicine And Precision Health Learning Health Care System

Implementing the principles of a learning health care system in a precision health program with an early focus on genomic medicine required multidisciplinary expertise coupled with a communication strategy that crosses traditional institutional boundaries to capture and integrate data from Geisinger and elsewhere.

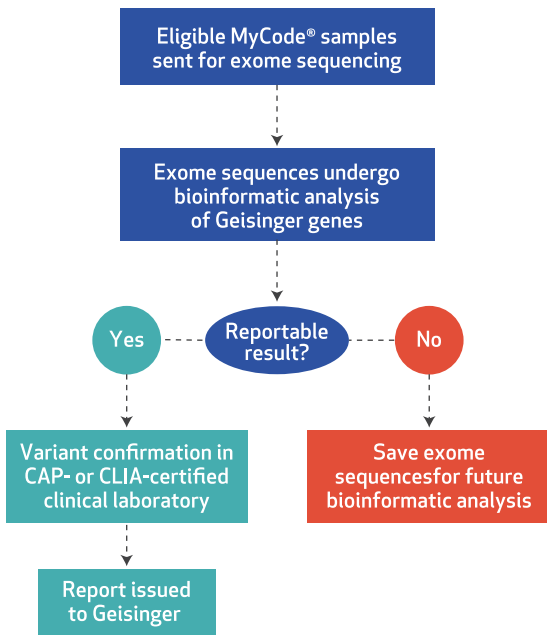
At the foundation of a learning health care system is an information system that uses data derived from the EHR but also captures critical data outside the EHR system. This includes collecting data from outside Geisinger, as the DNA variants identified by research exome sequencing must be confirmed in a clinical laboratory before being used for patient care. Data for the MyCode program are stored on local servers and in a cloud service that is compliant with the Health Insurance Portability and Accountability Act (HIPAA) of 1996 and the Federal Information Security Management Act of 2014. Business associate agreements are in place. All data stored on Geisinger servers are behind the system firewall and subject to Geisinger's security requirements. As the IOM has pointed out,[6] communication of genomic data among different systems has not been standardized. This has led Geisinger to create customized workflows to ensure that data are available for care and tracking. Details of the solutions are beyond the scope of this article, but it must be emphasized that the processes discussed below are dependent on a robust institutional informatics infrastructure.[15] While not all organizations have such an infrastructure, the increase in use of fully functional EHR systems coupled with international efforts to develop and implement standards to support the use of genomic data in the clinic should, in time, reduce reliance on local solutions to store and communicate genomic information and improve generalizability across health care information systems.

We next describe the initial overall workflow of the genomics and precision health program from research and innovation to clinical care, as presented in three phases: whole exome sequencing, data analysis, and variant confirmation; initial clinical care and support for results reporting; and transition to ongoing clinical care.

SEQUENCING, DATA ANALYSIS, AND CONFIRMATION Exhibit 2 depicts the process of transforming the research exome sequence for use in clinical care. The key component is the bioinformatic analysis of the DNA sequence to identify high-confidence, likely or known pathogenic variants that can be reported to participants and their providers and recorded in the EHR. MyCode participants are enrolled irrespective of any disease or condition, and interpretation of results must consider the low probability of a

EXHIBIT 2

Geisinger process for exome sequencing, data analysis, and variant confirmation



SOURCE Geisinger. **NOTES** "Geisinger genes" are explained in the text. CAP is College of American Pathologists. CLIA is Clinical Laboratory Improvement Amendments.

Assessment of the precision health program to identify and lower barriers to dissemination beyond Geisinger is ongoing.

person's having a condition associated with variants identified by the genomic analysis. Geisinger therefore uses conservative variant-calling protocols to minimize the return of false-positive results. For example, a variant in *BRCA1* (associated with hereditary breast or ovarian cancer syndrome) that has a high certainty of being disease causing (such as a three-star designation in the expert-curated Clinical Variant resource)[16] would be reported for clinical attention, whereas a novel variant would not be reported, as the clinical interpretation of such a variant has not been established by evidence-based best practices for variant annotation. When compared to diagnostic testing, interpretation of variants in the context of population screening is challenging for clinical laboratories. This is because diagnostic testing is performed for a clinical indication, which means that the patient has a high likelihood of having a disorder, so that variants found in a gene known to be associated with the disorder are more likely to be causal.

Variants classified as pathogenic or likely pathogenic by this process are further evaluated through the process of clinical confirmation. The exome sequencing in the Geisinger-Regeneron collaboration is not currently performed in a clinically certified laboratory, so variants must be confirmed in a clinical laboratory before the information can be used for patient care. By design, MyCode biospecimens are collected and maintained to comply with relevant clinical regulations, which obviates the need to collect another specimen, thus reducing the burden on each participant.

INITIAL CLINICAL CARE AND SUPPORT FOR RESULTS REPORTING The current process of informing patient-participants about their results is described below and visually depicted in the online appendix exhibit.[17] The process was developed in consultation with participants and providers across a range of specialties. Variants that are reported to patients are placed in the EHR using a scanned PDF laboratory report. Representation of the genes and variants in a form that is readable and hence searchable by a computer is maintained on a server behind the Geisinger firewall to support searching and follow-up. International standards for representing genomic data in EHR systems are in development. Once the standards are implemented in commercial EHR systems, the Geisinger process will be modified to use them, eliminating the need for local solutions.

Participants preferred for their providers to be notified first. A system was implemented to notify providers prior to notifying patient-participants, which allows the provider time to access materials relevant to conditions with which they might not be familiar. Online mini–continuing medical education courses and paired patient-provider interpretive reports[18] were developed for each condition category. The clinical genomics team—consisting of clinical geneticists, licensed genetic counselors, genomic medicine assistants, and support personnel—is available for consultation at the request of providers. Each patient-participant who receives a result must be contacted, to provide the opportunity to discuss implications of the result for their health care. This is done through letters and phone calls from a member of the team. Patient-participants who cannot be reached are sent a certified letter with the result, information about recommended care for the condition, information for family members, and contact information for the team. The team uses existing system communication channels for patient-participants whose providers are outside the Geisinger system so that the reports reach the providers.

Patient-participants are given the choice to follow up with their primary care or specialist provider, have a visit with a member of the clinical genomics team, or both. Because this care is provided as a clinical extension of participation in a research program, initial consultation with the team is provided at no charge to the participant-patient or third-party payer (costs are underwritten by Geisinger). A network of specialists and condition-specific clinics with expertise in disorders relevant to the genomic result works with the clinical genomics team to ensure the availability of evidence-based care for interested patients.

For the subset of patients covered by the Geisinger Health Plan, coordination with the payer ensures that any medical care recommended based on the reported result is considered medically necessary and is covered. The plan has also agreed to provide coverage for single-site genetic testing of relatives of the patients at risk of in-

heriting a variant, if they are plan members.

Communicating genomic results to at-risk relatives to support cascade genetic testing of these relatives enhances the value of the program. To empower patient-participants to communicate the genetic information to their close family members, the clinical genomics team requests the number of at-risk first-degree relatives and provide the appropriate number of copies of the result and a family letter. The team is available to support relatives considering testing.

A hallmark of learning health care systems is a commitment to continuous improvement. Two examples illustrate how continuous improvement cycles are used in MyCode to support genetic testing and reporting. One involves the development and implementation of processes for tracking the status of patients' original consent, to reduce the likelihood of contradicting participants' preferences.[19] Because the MyCode initiative is over ten years old, several versions of the consent document have been used. Older versions did not include consent for clinical use of results—a limitation noted when the clinical genomics team planned to report such results. This necessitated developing a process for obtaining reconsent from certain MyCode participants. While every attempt is made to get such reconsent, some participants have not consented to have results reported to their provider and uploaded into the EHR.

The second example involves managing information about people who have died since enrolling in MyCode, as a result may have value to the family of a deceased participant.[20] Since a participant's death can occur at any point along the MyCode program's pipeline, processes were developed and implemented to check the participant's vital status at multiple time points. At the request of MyCode participants and in consultation with the advisory groups, a procedure was developed to notify family members of a deceased participant and discuss results with them if they are interested.

TRANSITION TO ONGOING CARE To achieve the goals of a learning health care system, it is necessary to evaluate the impact of reporting genomic results to patient-participants and to the system. To help inform the process throughout Geisinger, the MyCode program leaders, in consultation with relevant stakeholders and advisory groups, have developed a set of outcomes (exhibit 3). Baseline conditions for MyCode participants can be established using historical EHR data that facilitate pre-post comparison of the impact of reporting results. Matched cohorts of Geisinger patients not in MyCode or who have no reportable result can be created to support prospective outcomes research.

For participants who receive their care from Geisinger, many outcomes can be captured from the EHR. Health outcomes might take years or even decades to measure (for example, familial hypercholesterolemia in the pediatric population). The stable enrollment of the Geisinger population provides an ideal opportunity to

EXHIBIT 3

Framework of outcomes for the clinical implementation of genomic information

Outcome type	Description	Examples
Process	Specific steps in a process that lead—either positively or negatively—to a particular health outcome	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	LDLc level at or below the target level of 100 mg/dL in response to interventions recommended based on 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	Decrease in myocardial infarction rates or cardiac revascularization procedures in response to interventions recommended based on 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 from self-reported health state and life disruption	Costs of sequencing and genomics results delivery infrastructure, direct costs of care related to return of genomic information and its use
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 in self-care, knowledge about gene and disease, access to recommended care, self-assessed well-being, family communication of genomic risk result, uptake of cascade testing

SOURCE Geisinger. **NOTES** LDLc is low-density lipoprotein cholesterol. *LDLR* is the gene that encodes the Low Density Lipoprotein Receptor protein.

measure the long-term impact of a precision health program.

Capturing outcomes data for patients who receive all or part of their care outside of Geisinger is more difficult but can be addressed in three ways: Claims data for Geisinger Health Plan members can be used to measure some outcomes. The Keystone Health Information Exchange, led by Geisinger, allows information from participating health care organizations to be collected for care coordination and research. Finally, patients are periodically contacted by the clinical genomics team after they have learned of their genomic findings. This provides an additional opportunity to collect information on patient-reported outcomes. Contact with patients is also critical to determining if the measured outcome can be attributed to the patient's learning about the genomic finding. For example, if a patient has a mammogram after learning of a pathogenic variant in the *BRCA1* gene, the mammogram could reflect disclosure of the variant or indicate routine preventive care undertaken irrespective of the variant. Accurate attribution of the outcome to the return of the result is essential to determining the true value of a precision health program like MyCode. At present, there are no standard approaches to determining attribution. This is an ongoing area of study for this and other precision health programs. Cost outcomes can be determined by applying standard costing methods to the clinical data. Outcomes are needed to populate economic models to examine the cost-effectiveness of the intervention and identify which data elements have the most impact on cost-effectiveness.

Clinical data can also be used to improve understanding of the impact of genetic variants on the risk of disease. These data are fed back into the sequence and data analysis process to improve variant annotation, creating a virtuous cycle—an essential element for a learning health care system. Variants reported to participants are also deposited into publicly available databases such as ClinVar.[16]

Closing the loop by developing processes to ensure the communication of results and defining and measuring outcomes is essential for any organization implementing precision health in the framework of a learning health care system.

Genome Screening As A Population Health Initiative

Geisinger has focused on several categories of conditions (encompassing eighty genes, referred to in exhibit 2 as "Geisinger genes") that met our initial, purposely conservative, criteria for clinical actionability.[21] It includes genes deemed reportable by the American College of Medical Genetics and Genomics.[22] The rapidly changing knowledge about gene-disease associations requires a process to reanalyze previously analyzed sequences and incorporate new knowledge about variants' pathogenicity. Approximately 3.5 percent of participants have a reportable variant.[12] As of January 2018, results had been reported to over 500 MyCode patient-participants.[23] Review of the metrics associated with the reporting process combined with input from the advisory committees allows Geisinger to identify opportunities for process improvement, and then to develop and implement these improvements. This results in increased capacity for reporting results and informs the new Geisinger National Precision Health Initiative.[24]

Early results from this program have been disseminated. Cases describing the impact of the program on patients carrying *BRCA1/2* pathogenic variants demonstrate the potential value of the program for participants.[25] While these anecdotal cases support the hypothesis that the program confers value, systematic analyses using pragmatic methodologies are under way to evaluate the value proposition on a wide scale. Studies in other organizations using standard methodologies are needed for replication and to assess the generalizability of the Geisinger findings.

Conclusion

This precision health program demonstrates two necessary conditions as identified by David Chambers and colleagues[26] for the convergence of implementation science, precision medicine, and a learning health care system: Clinical research need not be complete prior to implementation; and research and practice can—we would say must—coexist. These are central to Geisinger's vision of realizing the value of implementing a precision health program.[8] The approaches described in this article represent essential components that are relevant to any organization that considers developing a precision health program. Specific processes' generalizability to other settings must be evaluated in the context of local organizational factors, ideally using conceptual frameworks from implementation science. Assessment of the precision health program to identify and lower barriers to dissemination beyond Geisinger is ongoing.

A population-based approach to precision health that integrates implementation science and the principles of the learning health care system will be used to continually improve the value of the care delivered to Geisinger patients. ■

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