Rapporteurs: Jahnavi Narula, Ella Samer
Program Analysts, NHGRI

Genomic Medicine XIV: Genomic Learning Healthcare Systems
August 31, 2022 -September 1, 2022
Virtual
Meeting Summary

Welcome and Introductions

The Genomic Medicine Working Group (GMWG) convened leaders in genomic medicine to discuss the status of genomic learning healthcare systems (gLHS). The goal of this meeting was to discuss progress and identify generalizable solutions to genomic medicine implementation challenges experienced over the past 7 years, dating roughly since the 2015 National Academy of Medicine (NAM) *Genomics-Enabled Learning Health Care Systems* Workshop, and to examine persistent barriers and evidence gaps as opportunities for additional research.

The meeting opened with a brief overview of the 2015 NAM meeting, its outcomes, and how the present meeting will build upon it. Also overviewed were the outcomes of the previous 13 Genomic Medicine Meetings, including major publications and large consortium science advancements funded by NHGRI.

The objectives for this meeting included:

- Explore real-world examples of how genomic learning healthcare systems apply cycles of genomic medicine implementation, evaluation, adjustment, and updated implementation practices across delivery systems.
- Examine barriers and identify potential solutions, with a focus on lessons learned from effective gLHS and their potential transportability to other settings.
- Determine ways to develop and share solutions and form collaborations to facilitate research on implementing gLHS.

Session 1: Laying the Groundwork

An LHS is a health system where internal data and experience are integrated with external evidence. It involves continuous, iterative improvement; therefore, building an LHS requires a culture of that continuous learning and improvement. Leaders and providers must commit to that culture and find ways to make LHS sustainable. Additionally, a "data donor" culture must be facilitated, where patients are comfortable donating their genetic information for research. Patients should be treated as members of the team, and outcomes should be continuously assessed to ensure they are relevant and important to patients.

There are opportunities for research in gLHS implementation. Ideally, these research projects will include randomization as appropriate so the impact of gLHS can be tested in a rigorous way. Implementation of LHS is increasing, which opens the possibility of using implementation frameworks to systematically address barriers and facilitators for implementation, but currently they are underutilized.

Implementation of LHS requires investment in information technology (IT) to systematically gather and apply evidence in real time to guide care. An IT solution can share evidence with clinicians and capture

and analyze data to improve care. Scalable data science tools and knowledge bases are needed, and they must be effective across different organizations.

Incorporation of genomic information to create gLHS adds complexity to privacy and data sharing, and few institutions have fully implemented gLHS. Currently, there are differences in outcomes reporting, implementation methods, and precision medicine approaches for gLHS, which are barriers to identifying potential insights. Focus is increasing on incorporating genomics into the electronic health record (EHR), and personalized medicine programs are expanding.

Surveys sent to several gLHS regarding the organization and integration of genomic information yielded 10 responses. There was little consistency across them, with important differences in implementation noted such as differences in EHR modules and software, stages of integration, and metrics gLHS used for evaluation. Metrics more commonly used included health outcomes, health systems costs, and patient satisfaction. When formal frameworks were used for evaluation, they were usually CFIR or RE-AIM.

Survey respondents identified significant personnel needs for genomic educators, informaticians, genetic counselors, medical geneticists, and genomic medicine practitioners, but less so for pharmacogenetics. Solutions to fill these gaps included creation of a genomic medicine track in an internal medicine residency program, a Genomic Ambassador program providing peer-to-peer education to primary care providers, and a new genetic counselor training program. Training more medical genetics and genomics experts is difficult, however, due to a lack of candidates. One group also established a *Data Implementation and Science in Omics* unit to study models for translation of genomics to the clinic.

Significant obstacles to implementing gLHS included lack of bioinformatic infrastructure and lack of education of patients, clinicians, and systems (aligning with the expertise gaps noted earlier). Other cited obstacles were acceptance by patients, clinicians, and systems and the shortage of genetic counselors.

Potential solutions to these barriers included automated care pathways, creation and sharing of educational programs, developing a shared evidence knowledgebase and literature archive, establishing diverse and multi-institutional cohorts, and promoting transferability of longitudinal health data. While it is difficult for a system to create original educational content, care pathways, and clinical decision support, the Inter-Society Coordinating Committee (ISCC) and other groups are creating educational programs and can play a role in their dissemination. Sharing such programs may be key to improving education, although sustainable models are needed for how that information will be shared.

Discussion

Panelists briefly described implementation of specific gLHS projects and barriers and potential solutions to gLHS implementation. Challenges included: patients who receive actionable genetic results may not receive appropriate follow-up; results may become actionable well after the initial testing is done, so ongoing monitoring and follow-up are needed; and technological solutions for assisting providers are needed. Implementation frameworks for developing solutions are key, and care is needed to ensure workflows meet the needs of providers and patients. Creative solutions could include utilizing non-genetics infrastructure, such as providing family history screening during mammogram appointments.

One discussion topic was use of “third-party” genetic counselors. One institution saw rates of notifications and consultations go down when third-party genetic counselors were employed. While this could be due to a decline in engagement over time, it is also possible that use of third-party vendors makes navigating the healthcare system more difficult for the patient, despite being more efficient for the system.

Operational details also greatly impact gLHS. Their impact can be mitigated by using an implementation framework, interviewing stakeholders engaged with the process (such as schedulers), and using dashboards or other monitoring tools and standardized metrics. Unfortunately, many of these monitoring processes are not automated and are labor intensive; however, improved tools can help.

Several models were discussed for funding gLHS, including self-support from within an institution, partnerships with industry, state sponsorship, and combinations of these. While gLHS do cost money, these programs can also attract patients and improve quality of care.

Health disparities can be mitigated in gLHS by leveraging close patient-provider relationships and providing low-tech approaches to return of results if those are needed. Solutions to returning results requiring internet or smartphone access, such as an app, will likely increase disparities. Having a community champion may help with engagement of underserved populations. Monitoring genotype and clinical data to ensure benefits and harms of the gLHS are as balanced as possible across groups is key.

Transferability and interoperability of genomic data across health systems is also key to gLHS implementation. One possible solution is putting data in the hands of the patient, so that patients carry data from system to system as they move, recognizing that there may be specific local software standards. Interoperability is a significant issue for genomics, as genomic data can theoretically last over a lifetime.

Main takeaways included the importance of monitoring uptake of genomic-based health recommendations, improving the quality of that process, and doing no harm, especially in pursuing the goal of increased diversity of the evidence base. Merging genomic data with not only clinical data but also social determinants of health should also be a focus, as should understanding the economics of this process and convincing payers to pay for genomics-based care. Finally, EHRs should improve integration of genomic data and broaden the utility of those data once present; interoperability across EHRS will be key.

Session 2: IT Infrastructure

The session started by reflecting on the big ideas generated during Genomic Medicine XIII: Developing a Clinical Genomic Informatics Research Agenda in February 2021. Goals of that meeting included: 1) defining the current status of genomic-based clinical informatics and related knowledge gaps, 2) determining facilitators and barriers that affect the development deployment of genomic-based clinical informatics resources and research, 3) identifying research needed to improve how genomic-based clinical informatics resources impact patients and the clinical decision making process, and 4) developing research strategies for the use of genomic-based clinical informatics tools and resources. Other relevant themes included the importance of collaboration (specifically with patients) as well as supporting research that informs business models and promotes open-source development.

Integrating genomic results into EHRs will depend upon establishing data standards/data sharing and using a precision medicine framework that moves from individual patients to patient populations and population health. A great example of this is PREDICT: Personalized Medicine Initiative at Vanderbilt University Medical Center (VUMC), which is now tracking 20 drug-gene interactions to help optimize drug treatment. In this model genomic results data and raw files can be stored in the VUMC EHR and operational data storage sites. This process allows for increased uptake across health care systems and provides structure in the EHR. Once data are uploaded in the EHR they become immediately accessible to patients and providers, allowing for a more patient-centric approach and opening possibilities for patient

education. This approach increases the accessibility of data through the VUMC EHR and reduces the time needed to get information to the provider from weeks to hours. Such a program could be explored for its potential impact at a population level as well as the individual patient level, and on EHRs across multiple health systems.

Major goals of population-based clinical decision support in precision medicine included: 1) establishing a platform for population health management that will identify and manage risk, 2) leveraging family health history in the EHR, 3) minimizing burden on patients and providers, and 4) leveraging automated chatbots for patient outreach. The BRIDGE trial at the University of Utah and NYU is comparing patient-directed vs. standard of care approaches to providing genomic results. Genetic Counseling Assistants and chat bots are additional ways of increasing outreach and education.

In summary, this session highlighted the very early stage of development of most genomic IT resources, but also the considerable progress that has been made by paradigmatic early-adopter systems. Such systems have the potential to perpetuate and exacerbate genomic health disparities, and equity should be built into systems from the start.

Discussion

Genomic health information exchanges across health systems were seen as potential solutions to these challenges, as were accepting and broadly adopting single standards and methods, expanding interoperability, facilitating data sharing, creating national policies around genomic reanalysis for care, expanding genomic training for clinical providers, and addressing the potential for gLHS to exacerbate health disparities and further isolate underrepresented communities.

Resources like the 'GenomeX' Project could help in accelerating genomic-EHR integration and data integration. New initiatives at NICHD focusing on linking parent-child medical records and generating higher quality family medical histories could help increase the data available for medically underserved communities and combat health disparities related to EHRs. NHGRI is also reallocating efforts to engage underrepresented populations through new funding opportunities.

The need to increase efficiency in providing genetic counseling through telemedicine and/or chat bots raised questions related to insurance and coverage, language barriers, accessibility to technology, cultural updates, patient and provider education, and quality of care. Chat bots can be used as an initial resource or educational tool, as well as a tool for outreach. They can also free up time for genetic counselors to spend with patients, focus on education, and provide quality health care.

Having quality genomic/genetic education for health care providers and patients was a key theme in this session and throughout all sessions of the meeting. Patient as well as provider education paves the way for sharing information immediately with patients and facilitating patient-centric approaches.

Session 3: Increasing Health Access and Equity for Genomic Healthcare

Many types of bias may cause gLHS to produce rather than reduce potential health inequities, some of which may be built into automated learning systems, such as automated healthcare support tools. For example, using variables such as race and ethnicity that are strongly associated with social determinants of health (SDOH) can lead to race/ethnicity being falsely identified as risk determinants. In addition, pathogenic genomic variants may not be equally frequent or penetrant in different populations, and such variants and the subgroup of individuals carrying them can then be misclassified as "high-risk." Biases in

EHRs can also be problematic, such as missing data that are more likely to occur in patients who switch medical systems and those with low health literacy. Such biases disproportionately affect minoritized populations, as do problems of small sample sizes and increased measurement error.

Race has been misused as a variable in risk prediction scores, which can lead to misclassifications of risk and potential inequities in medical care. Instead, relevant genotypes can be used to predict risk instead of race and models assessed with C-statistics, positive predictive values, and calibration. Models can be debiased through *reweighing*, or taking variables such as race or level of privilege into account, and *relabeling*, or pulling out variables that may confound the algorithm. Leveraging the gLHS feedback loop to monitor and evaluate incoming data can pave the way for equity-focused gLHS.

Inequities in biomarker research can also affect all stages of the translational pipeline. Seventy-one percent of all genomic cohorts from two key databases are focused only on populations of European descent, even though 85% of the world's population is of non-European descent. This impacts genetic testing in several ways. Biomarkers can be missed in non-European populations, and as a result, genetic testing may be less effective and less safe for those populations. Genetic testing may also be less generalizable and accurate, which affects its translation to practice and to communities.

A focus on equity research is also needed in the later stages of the translational pipeline, where gLHS can be used to research equity, diversity, and disparities. This should be implemented with a learning, monitoring, and systematic evaluation system that engages diverse stakeholders and coordinates implementation around diverse healthcare settings and populations. For data on equity to be captured, equity must be built as a central part of a gLHS.

Team science can facilitate equity by involving researchers, patients, and clinicians together in decision-making. This will result in a better understanding of potential issues, better-designed studies, and better outcomes. Creating a patient-centered gLHS involves putting the data in the hands of the patient. By leveraging HIPAA, patients can consent to have their genotype and phenotype data linked and shared. Clinical data can also be obtained by using machine learning to extract data, both from the EHR and from health information exchanges. Leveraging federal information blocking rules can also help with obtaining data from health information exchanges, as patient-partners are entitled to access their data and can share it as they wish.

Discussion

Defining "genetic ancestry" is complex and continually evolving, with race commonly used as a proxy. While race is a social construct or an experience, it affects health outcomes. When defining race and racial bias in international settings, it is necessary to think about how each population will experience race and racism. Ideally, international studies should capture race in a contextually appropriate manner.

Building capacity for diverse research is necessary to ensuring equity in gLHS implementation; there are no gLHS in historically Black medical schools, for example. Intentionally focusing on infrastructure and capacity-building at these institutions is essential to building equitable gLHS. The NIH and NHGRI have been proactively pursuing opportunities in engagement, but more can be done, such as increasing funding towards advocacy groups and having them set research agendas. It was suggested that NHGRI prioritize engagement in RFAs and set aside a budget specifically for engagement.

Equitable access is also needed to ensure equity in gLHS, including access to care, to an individual's results, to their detailed genotypic and phenotypic data. Patient involvement with the research design process can help understanding patients' barriers to access, as through a core patient group, representative

of the patient population, who can work with the research group long-term. Listening and learning from various patient and clinician groups through active engagement such as focus group is also helpful.

Engagement also involves education. Patients should not only be able to access their own data but should also be able to interpret their data and will need tools and education to do so.

The important takeaways from this session were: 1) continuously assess the equity of the gLHS being implemented, 2) create measurable outcomes for assessing equity, 3) build a platform in which equity is a central part not an afterthought, and 4) ensure equity efforts are meaningful and avoid *equity fatigue*, and 5) make equity central to research, sustainable, and adequately resourced.

Session 4: Enabling Providers to Implement Genomic Knowledge

The importance of education for medical staff, particularly primary care physicians, and patients was a consistent theme in this session and throughout the meeting. The Icahn School of Medicine at Mount Sinai is contributing to this space by establishing a new genomic medicine track in their internal medicine residency which was launched in July 2020. This track exposes residents to genomic medicine, cancer genomics, cardiovascular genomics, pharmacogenomics, genomics and population health, polygenic risk scores, genetic ancestry, and gene therapy. Residents have also expressed interest in a fellowship which would further expand their education in genomic medicine.

Training in genomic medicine can be further expanded to include bioinformatics, IT, genetic counseling, medical ethics, compliance, clinical operations, and research strategies. These topics both add to the curriculum and benefit the system as a whole by facilitating implementation for large health care systems.

With advanced genomic medicine education, we also need to help frontline medical providers utilize genomics and genomic information in a meaningful and efficient way. To see real implementation, there needs to be institutional investment (resources and support), uniform standards/strategies, and team development. Several examples demonstrated how clinical geneticists offered support and resources to physicians to address complicated cases and provide high quality care, demonstrating how support, education, collaboration, and implementation can improve patient care and outcomes.

VUMC has developed an implementation strategy (mentioned in session 2) that provides a Genetic Test Ordering Consult (GTOC). This helps front-line providers determine how and what to order, and accurately interpret the results and provide necessary follow-up. GTOC leverages resources already in place at VUMC to educate and build the confidence of front-line providers. The GTOC can pull information from VUMC's reference lab system and can also contribute to research efforts. Once tests are selected and results are received, they are immediately uploaded to the EHR for use in patient care.

Genetic counselors are also a key part of the medical team and are crucial to providing patient education and outreach. Johns Hopkins has a research project examining a genetic counseling model that has more focus on post-test genetic counseling than on pre-test. Video education is used to supplement pre-test education. This approach increased patient satisfaction and genetic counseling efficiency, specifically in specialty medicine, as well as increasing patient empowerment, engagement, and risk perception.

The Veterans Health Administration (VHA) works to increase healthcare access for Veterans, including access to high-quality clinical trials. The VHA's innovations ecosystem enables discovery and spread of mission-driven healthcare innovation, exemplified by the PHASER pharmacogenomics (PGx) project. As the largest known PGx project, with a goal of reaching 250,000 Veterans, it aims to provide an end-to-end

solution for implementing panel-based PGx testing. The VA's Million Veteran Program also advances precision health care through learning about genetics, lifestyle, and how military experiences affect health and illness. With over 900K Veterans enrolled, it will be the world's largest genomic database.

Discussion

The participants and panelists were impressed with Mount Sinai's genomic medicine track but had questions about sustaining awareness and sharing curriculum with other institutions, as well as the format of the track and how residents were able to participate within their complicated schedules. The track includes virtual, pre-recorded, and in-person options; more information will be provided in follow-up.

Educational opportunities should be expanded beyond physicians, as nurses, physician assistants/associates, medical assistants, pharmacists, and genetic counselors play important roles in patient care and education. Creating 'genomic medicine boards' similar to tumor boards can also increase access to and understanding of genomic information. A board of experts made available to colleagues both local and remote can consult on cases and educate in the process. A board or boards could also develop listservs, disseminate monthly case conferences, and provide regular updates across systems. Improved integration of genomics into EHRs could also allow a range of providers to access the same information and services.

One barrier is that Medicare, and thus insurance companies, do not recognize genetic counselors as reimbursable providers. VUMC and many other healthcare systems have decided to support the cost of genetic counselors as an essential resource while working to promote their eventual recognition and reimbursement. Figuring out how to increase access to genetic counselors is something all groups should work to solve.

Sustainability and access to different programs were emphasized throughout the discussion, as was the importance of institutional support, collaboration, interoperability, and education not only for patients and providers but for institutional leadership. Leveraging national and state support is essential for increasing access to genomic medicine and could also lead to policy changes that allow for broader implementation.

Many institutions are willing to share their system design and work with others, and eager to learn how to automate some of the processes. Building the best systems possible will require different groups to collaborate and share rather than devoting time and resources to something perceived to be proprietary.

Session 5: Establishing and Sustaining gLHS

Several health systems are making LHS work, such as Intermountain Health. Its over 200 caregivers distributed across the intermountain region provide precision medicine services, including to rural communities, to promote more equitable access. Intermountain's precision medicine focus includes somatic testing, PGx testing, genome sequencing, and population health. Recognizing that just having genomic data is not enough, providers also need to be able to explain the data and understand the implications, a constant focus of Intermountain's efforts. Another important issue is to understand the cost of gLHS and demonstrate its economic feasibility and benefits for the system and patients. One example is the precision oncology unit where the gLHS saves $734 per patient every week, a huge impact. Intermountain predicts their gLHS can save $50M a year in implementation costs. Their HerediGene: Genomics of a Single Population project of 500,000 patients over 5 years is designed to identify areas where cost can be reduced. This project is not just research, but rather a full integrative loop

where patients receive results, referrals, and treatment if needed. Intermountain is letting patient care as well as economics drive their system and are finding lots of success from these efforts.

Payers and gLHS need to think differently about policy and coverage. Although coverage is determined by each insurance company, each insurance company sets its own policies, and policy does not equate to coverage. United Healthcare and its information and technology company, Optum, are increasingly recognizing the large economic burden of rare disease. Rare disease is expensive and getting a diagnosis can be extremely difficult, but Optum is working to change this by making policy changes on a personal and national level. They are also looking at the relationship between research and policy, and how genetic testing and availability play into this relationship. Economics and insurance components of a gLHS are important to sustainability but are often opaque and need to be understood more fully.

The Personalized Medicine Coalition is working to achieve a broader adoption of personalized medicine (PM). They've developed a novel 'maturity model' with specific metrics that objectively measure PM adoption and provide key information about the state of the health care system. The 153 organizations rated included PM implementers across a variety of health care systems, academic affiliations, and regions. They were scored on a scale of 1-8 with 1 being low adoption of PM. Most systems that were part of the study were scored 2 or 3, with considerable work needed to get groups to an 8. Such a scoring system provides crucial benchmarks and helps systems set tangible goals for improvement.

Discussion

Key decision-makers must understand the economic value of personalized care so they appreciate the promise of gLHS, but showing economic benefit requires long-term studies, and evidence is still sparse. If cost-effectiveness is demonstrated, Centers for Medicaid and Medicare Services alternative payment models (APMs) could be used to promote adoption, as APMs incentivize payment for provision of high quality, cost-efficient care. Additionally, most health economic outcome studies look at 12–17-month outcomes, not long-term outcomes, so showing the short-term benefits of personalized care will be necessary. Following long-term patient outcomes across insurers may also be helpful. A proposal like the Medicare Coverage of Innovative Technology (MCIT) can be useful for coverage.

As wide-spread population screening becomes more feasible, it is necessary to understand how to pay for medical services that under- and uninsured patients may need. The Genetic Nondiscrimination Act (GINA) protects patients with a genetic variant who have not yet manifested the disease, but by the time a genetic test is done, patients may already have a manifestation of the disease. This is the case for 20-80% of patients at Geisinger, depending on the disease. The value of genetic population screening, as opposed to at-risk screening, still needs to be demonstrated to payers.

In terms of coverage for PM screening, there has been some success with Medicare Advantage plans as opposed to direct Medicare coverage. Medicare Advantage also allows for coverage of preventive services not covered by Medicare. Geisinger's system enables assessment of whether preventive medical services derived from variant identification are good uses of Medicare Advantage's preventive funds. Geisinger has an integrated system, meaning a loss on the insurance side can be sustained if it's recovered on the care delivery side. Independent insurers, in contrast, will only see the cost and not the savings. Aligning the strategies and values of these different organizations will be challenging but is essential.

Clinical effectiveness of engaging individuals in meaningful care after receiving a result also needs to be measured, in addition to the economic effectiveness. Typically, studies are designed to determine both cost and clinical value. The most important thing to the patient is often clinical utility but this is difficult to study; gLHS can help address this. Additionally, a "net promoter score"—a score of patient

satisfaction—can be useful when thinking about what meaningful care and utility are to patients. In terms of sharing data, there should be a balance between informing the field and not compromising an institution's ability to move forward. A forum to share these findings may be useful.

It is necessary to show payers that there is value in gLHS. This could be facilitated by including a payer advisory group, establishing collaborations with payers and having more direct interactions with them. The leaders of gLHS have largely been integrated systems in part because the payers are within the system making collaboration easier. Engaging with payers outside a system is much more difficult, but there are ways to do so, such as partnering with Optum to examine their vast data sources. Another possibility is engaging a health system partner such as a local network or large company.

Valuable takeaways from this session included the need for data showing how precision medicine reduces cost and improves outcomes and for clear guidelines to help payers make decisions. Collaboration with payers could help with this. Additionally, outcome metrics for precision medicine adoption are important.

Session 6: Realizing the promise of gLHS

To realize the promise of gLHS, the current genetic testing workflow must change. An idealized workflow would include the lab receiving full clinical data and/or access to medical records rather than an often-one-word diagnosis or no diagnosis at all. For likely pathogenic (LP) variants or variants of unknown significance (VUS), the lab should investigate further. Pathogenic (P), LP, “VUS-high” or VUS variants with a strong phenotype match should be reported, and *structured* genetic test results transmitted to the EHR with an accompanying patient- and provider-friendly report. The relevant variants, with new evidence, should be submitted to ClinVar. This idealized workflow depends on the ability of the lab to access phenotypic data on the patient, and the ability for the provider to give feedback on candidate variants. It also requires resources such as a globally shared database of individual-level genotype and phenotype data, a functional database with high-throughput analysis of all hypothetical variation in each gene, and familial genotype/phenotype data.

Building a gLHS with this ideal workflow will take many elements. IT solutions with feedback or interaction “loops” from the provider to the lab and back to the provider are critical. Standardized genotype representation and data storage, meaningful and standardized phenotype collection, infra-structure (and willingness) to share individual-level data globally, improvements to standards and quality metrics, and reciprocal collaboration between the lab and provider are all needed to realize this ideal.

Patient engagement is key to building a gLHS. Ideally, personalized medicine maximizes outcomes the patient cares about most and minimizes those the patient fears the most. Patients should thus be engaged before the project is initiated to define key questions and important problems. They should also be involved in an active partnership, including in analysis and interpretation of research and quality issues. Outcomes should not only be patient-centered but also patient-informed. Although this will require added time and effort, patient involvement will improve the relevance and ultimately the value of this research.

Scalability is a key issue in trying to create a national gLHS. Systems that are siloed are not scalable, so ensuring EHR interoperability is key. This requires genomic data to be standardized, accessible and clinical-grade. Policy or regulations may be needed to make EHRs fully interoperable for genomic information. Currently, GA4GH and HL7 are working on data standards and interoperability.

Clinical decision support (CDS) is also needed for real-time care and gLHS. Implementing genomic CDS requires a consensus on allele and test code nomenclature for standardization, a shared warehouse of CDS tools, a core infrastructure to disseminate CDS, and clinical trials to assess impact of CDS on outcomes.

Standardization, consensus, and sharing of gLHS knowledge require platforms with reusable components that follow FAIR principles so data can be re-used, as well as creating a "data donor" culture among gLHS. Integrating patient-provided data into healthcare IT systems, accessing data from multiple sources to increase study size and power, and supporting research to understand and generate personalized user interfaces and preferences are also helpful. Little effort is currently expended on building platforms with FAIR principles and engaging the public. In addition, patient-provided information is typically not used, and phenotypic data generated from EHRs usually have gaps.

A potential model for a national, scalable gLHS is NIMH's Early Psychosis Intervention Network (EPINET), which established a culture of collaborative research participation and involves data sharing through a central coordinating center. It includes standardization of clinical characteristics and interventions, outcomes, strategies, data elements; use of informatics to study variations in treatment quality, clinical impact, and value; practice-based research; dissemination of information to scientific, patient, and provider communities; and sharing tools, data, and best practices as critical elements.

To apply these elements to genomics, genomic and precision medicine clinics nationwide need to be identified and a network created. Stakeholders such as payers and patient advocacy groups should also be involved, perhaps through a coordinating center supported to gather data on genomic medicine in practice, quality improvement, and benchmarking. The *All of Us* Research Program could be leveraged as a national research platform due to its scale, accessibility, and diversity. Though gLHS exist across the nation, they are operating independently and many are siloed; this might enable scaling them to a national level.

Discussion

Providing individual-level phenotypic data with genetic testing requests could produce false positive associations because of the lack of phenotypic data in negative control phenotypes. Over half the causal variants found are unique to one family, so there is no option but to use whatever phenotype data are available. For common phenotypes, case-control studies can be used as they are in PGx studies.

Sometimes the outcomes patients care about are not the outcomes payers are willing to pay for. For example, in rare disease, a diagnosis does not necessarily change outcomes but can be beneficial to the family. The importance of personal utility versus broader clinical utility is difficult to assess. Payers are reluctant to pay for genomic testing solely to end the diagnostic odyssey even though genomic tests can reduce the costs incurred on the diagnostic odyssey; the ability to end it should be viewed as an economic gain. The genomics community needs to focus on what it can do rather than what it cannot yet do. Communicating that genomic tests do change care and identify better treatments will be essential.

Summary and next steps (see executive summary for more details)

Several opportunities for facilitating the creation and implementation of gLHS, and for collaboration among them, have been identified. Automating clinical management steps; improving genomic health information exchange across health systems; linking clinical and genomic data within health information exchanges; expanding interoperability; ensuring meaningful, ongoing, high-level patient engagement and

measuring its impact; creating dynamic, iterative workflows between providers and labs; and integrating institutional variant review committees into the gLHS workflow will all contribute to facilitating gLHS.

gLHS can collaborate on developing, assessing, and implementing specialty tracks and consult services, which can also help to improve access in low-resource settings. Creating a monthly case conference and/or a virtual “molecular board” would help to create a learning community. Systems should collaborate to demonstrate economic benefits and improved outcomes of genomic medicine, potentially through creation of a national gLHS network. Research priorities that could be pursued by such collaborations include defining and measuring patient-informed outcomes and engaging payer advisory groups in developing clinical utility studies. In addition to this meeting summary, GMWG will consider creating a white paper to summarize recommendations and future directions for gLHS implementation.