



Genomic Medicine XIII Developing a Clinical Genomic Informatics Research Agenda

Summary Report



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Genomic Medicine XIII: Developing a Clinical Genomic Informatics Research Agenda

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Virtual

Meeting Summary

Welcome and Introductions

The Genomic Medicine Working Group (GMWG) convened leaders in genomic medicine to provide guidance to the National Human Genome Research Institute (NHGRI) in developing a research agenda on genomic-based clinical informatics tools and resources. The goal of the meeting, titled “Genomic Medicine XIII: Developing a Clinical Genomic Informatics Research Agenda,” was to develop a research strategy on the use of genomic-based clinical informatics resources to improve the detection, treatment, and reporting of genetic disorders in clinical settings. The meeting had the following objectives:

- to define the current status of genomic-based clinical informatics and related knowledge gaps
- to determine facilitators and barriers that affect the development and deployment of genomic-based clinical informatics resources and research needed to address them,
- to identify research needed to improve how genomic-based clinical informatics resources impact the patient and clinical decision-making processes.

Presentation of the 2020 NHGRI Strategic Vision

In October 2020, NHGRI published “Strategic vision for improving human health at The Forefront of Genomics” in *Nature*. Dr. Eric Green, Director of NHGRI, noted that since the Strategic Vision could not possibly cover the entire field of genomics, the Strategic Vision focuses instead on “The Forefront of Genomics.” This vision signals a new era in genomics for the institute and the field by describing the most compelling research priorities and opportunities in human genomics for the coming decade. The 2020 NHGRI Strategic Vision recognizes that responsible stewardship is a central aspect of being at (and pushing forward) the forefront of genomics. The vision identifies four focus areas: 1) Guiding principles and values for human genomics, 2) Sustaining and improving a robust foundation for genomics research, 3) Breaking down barriers that impede progress in genomics, and 4) Compelling genomics research projects in biomedicine.

The Strategic Vision culminates with ten bold predictions for human genomics by 2030. The predictions were crafted to be inspirational, aspirational, and intended to provoke thoughtful discussions (and even debate) about what might be possible in the coming decade.

Session 1: Making The Case for A Clinical Genomic Informatics Research Strategy

In a survey sent out about genomic-based clinical informatics tools and resources, respondents agreed that methods for integrating analytical interpretations derived by computational models of genomic data into clinical settings are not well established. Respondents also rated 1) support for the integration of genomic and genomic-related information into the electronic health record (EHR) by the Centers for Medicare & Medicaid Services Promoting Interoperability Programs, 2) advancements in storing genomic and genomic-based information to meet the needs of the

clinical genomics community, and 3) business models for developing and implementing genomic-based clinical informatics tools and resources to encourage open source development as top priorities in the field. Other relevant themes included the importance of assessing stakeholder preferences and workflows, sustainability of resources, the need for methods for evaluation of innovation and implementation, and the impact of the consent and regulatory framework. Any research agenda should pay particular attention to these topics.

Furthermore, any research agenda regarding genomic-based clinical informatics tools and resources will need to address elements described in Masys et al.'s published technical desiderata to integrate genomic information within the EHR[1]. The NHGRI has supported efforts, through its extramural programs, that have led to satisfying most of the outlined desiderata. Even though several remaining elements in the desiderata still need to be addressed, the survey results indicate revisions to the desiderata can benefit the genomic medicine community. Such modifications should include developing an architecture to access genetic and genomic sequencing information from the EHR directly. Specifically, a new framework to classify and synthesize genomic-based clinical decision support (gCDS) implementation into healthcare systems may be required. For example, the NHGRI funded Electronic Medical Records and Genomics (eMERGE) Network's EHR integration (EHRI) workgroup has identified 25 potential hazards relating to gCDS implementation that investments are needed to resolve[2]. The eMERGE Network published a series of articles regarding these hazards and lessons learned in the implementation of gCDS[3-5]. Different decision support types should be considered when developing a research strategy in genomic-based clinical informatics tools and resources. Efforts by vendors and members of the clinical genomics community utilize Fast Healthcare Interoperability Resources (FHIR) standardization and data harmonization to address these current challenges. However, FHIR was not designed to address the needs of genomic-based clinical research. Efforts will be required by both vendors and the clinical genomics community for FHIR to serve in that capacity.

Finally, any clinical genomics research, including related informatics tools and resources, must acknowledge how race impacts clinical genomics and the clinical implementation of genetic information. For example, Black patients are less likely than White patients to be referred or included by default into screening programs based on observed genetic risk even after adjusting for disease-specific population allele frequency. Total medical expenditures per capita are roughly similar between Black and White populations even though Black populations are sicker. Dr. Janina Jeff noted science is as socially and politically constructed as any other field. Bias in medicine and medical documentation with origins in the eugenics movement is pervasive in how it impacts data, knowledge, infrastructure support in EHR systems, access, and value definitions. The field of genetics must be willing to confront its sordid eugenics-oriented past, actively strive to be anti-racist, and proactively seek to identify and remove inherent biases that affect data and systems used for research and clinical care. It must seek out reviewers from a diverse range of backgrounds and experience, monitor for discrimination arising within a scientific review, establish robust equity policies, have developers work with patient engagement groups, and recruit and retain scientists that reflect society as a whole. Specific to this meeting's topic, the goal of clinical informatics and EHR integration of genomic and its related information should be to support research that proactively and explicitly addresses systemic biases in data, information systems, and clinical care delivery.

Discussion

Given the amount of information, research into the prioritization of data most important to patients and clinicians and promoting its integration into the EHR (such as high impact genetic variation and Center for Disease Control and Prevention's Tier 1 conditions) is needed. It is also essential to reanalyze exome sequences over time. When new clinical information about a genetic variant becomes available, the latest information should be integrated into the EHR. Research is also needed to understand the best ways to accomplish this complicated process. Clinical informatics also needs to explore approaches to implementation more fully, emphasizing research on genetic information that has already been shown to have clinical utility. More broadly speaking, different institutions' needs and capabilities must be considered when developing a comprehensive research strategy. Low-resource institutions need different kinds of tools and support than high-resource institutions. More research must be done to determine how best to support the implementation of gCDS tools in low-resource institutions. The concept of 'implementation equity' is an essential topic for research and funding. Opportunities should promote engagement across many different types of systems to reduce this inequity.

The collection of samples and generation of data from diverse populations is essential to genomics research. When it is not possible to leverage a highly diverse population of samples, existing models must be refined to reflect the realities of different subpopulations accurately. As important as it is to collect samples from diverse populations, that benefit has a risk of being made moot if the analysis (including algorithms developed to assist investigation) is inherently biased to impact the study results. Data science has made some progress in correcting such biases, as in addressing racism in many predictive policing algorithms; however, it will take a great deal of work to write new, equitable algorithms. Any new algorithm must be tested repeatedly for inherent detrimental bias by ensuring that training data includes samples from highly diverse populations. Research into methods to identify and eliminate inherent detrimental bias from algorithms is needed. The general public has a lack of information about clinical informatics and genomics. For example, much of the engagement with Black/African American communities center around ancestry in genomics. There must be transparent conversations about the full spectrum of genomic research and what, if any, benefits there may be to the participants. Most people choose to participate in scientific research from a sense of altruism. However, the scientific establishment must recognize that this is a privileged outlook and maybe unappealing to communities that have been historically and systemically taken advantage of by the scientific and medical communities.

Equity also requires a rethinking of the research infrastructure. Researchers must be partners with participants and their communities. Research projects should also promote value for both researchers and participants. Although this new paradigm would undeniably add another layer of complexity for the researcher and institution, new evaluation frameworks are needed to draft an equitable genomic research strategy.

Session 2: Need For Research In Advanced Technologies (AT) To Support Genomic Medicine

In genomic-based clinical informatics, 4-5 years ago, there were few defined standards and a need for pilots to define and test standards. In the United States, healthcare is not well integrated across multiple providers and settings, so the patient is the only consistent presence across the healthcare system. Genomic sequence data have the potential to be used across a patient's lifespan. Still, the data are generally not associated with the patient (patient-centric) but instead

are held by a health system, laboratory, or both. A patient-centric approach to genomic data is desirable. Presently, patient-centric standards have been developed from pilot studies. Scalability is key to taking the next step in this area. Other needs include interconnectedness; Artificial Intelligence-ready, research-ready genomic medicine; a networked ecosystem, addressing security and privacy concerns while still promoting research; empowering patients; and promoting diversity. A consortium could convene organizations around these needs to create sustainable and scalable infrastructures to support genomic data collection and use. Various applications could apply standardized genomics modules for use by patients, physicians, or patients and physicians together. For example, The Diabetes Electronic Medical Record (DB EMR) integrates clinical, genomic, and sensor information and includes the Substitutable Medical Applications & Reusable Technologies (SMART) Genomics Advisor[6]. The SMART Cancer Navigator implements the American Society of Clinical Oncology (ASCO) Workshop Recommendations to Enable Precision Cancer Medicine was also highlighted. Individuals are empowered via smart contracts wherein they decide what data they would and would not like to have shared with themselves, family, other individuals, or in research. It is essential to work toward an ecosystem where the different pieces are interconnected and working together[7]. A clinical example from the Undiagnosed Diseases Network (UDN) at Vanderbilt University Medical Center (VUMC) highlights how EHR integration can improve genetic medicine. A patient had a de novo frameshift mutation in a gene that was not known to be associated with the disease. An EHR search of over 3 million patients identified two patients with de novo variants in the same gene. A chart review of these individuals revealed phenotypic overlap with the UDN patient providing additional evidence that this gene was associated with the syndrome and the variants were causal. This approach is potentially replicable. A clinical genetics database that includes information about genes tested, genes found, variants, zygosity, and interpretation accessible within the EHR ecosystem would make searching for matches much easier. Currently, this information is stored in PDF genetic reports and is sometimes entered in patient charts as free text. VUMC undertook an effort to index their medical records by genetic findings. It was found that the results get entered in various places within the EHR, so there can be no fully automated way to extract this information at present. Genomic sequence information generated through clinical testing but reused for additional indications is essentially free—if the information systems can access and use the information. This process is relevant because the number of patients with genetic findings in their EHRs is increasing, the pathogenicity of variants can be determined, and observing variants at a population level can provide a new perspective. Researchers could be exploring these data, however, extracting the information from the EHR will have to be institution-specific.

Developers and implementors will need to understand how medicine is progressing to achieve genome-friendly care tools and resources. The COVID-19 pandemic has influenced a quick acceptance of telemedicine, which will likely remain in practice. Medicine is also accounting for social and behavioral determinants of health and genetics, and the emergence of artificial intelligence (AI) will impact practice. Efforts that enable medicine advancement include FHIR, The 21st Century Cures Act, and various AT. These advancements can be leveraged to achieve a goal of having both health system and patient satisfaction with genome-informed care, but there are barriers to this. Health systems face challenges regarding interoperability, data flow, provider knowledge, information literacy, and investment return. Patients face challenges regarding equity, literacy, fear, and misinformation. There are also questions of addressing genetic discrimination fears and determining what can and should be automated. Research needs to be

aimed at addressing these challenges and questions.

Discussion

Scaling patient matching queries outside of individual institutions is a significant barrier. Gene matching would be made easier with large, interoperable databases. However, many databases are rich in genotypes while poor in phenotypes. Though Online Mendelian Inheritance in Man (OMIM) has been annotated with Human Phenotype Ontology (HPO) terms, it is not enough to address the clinical genomics community's needs. Even if there was ample phenotypic information that is both standardized and harmonized (which it is not), it is difficult to extract such information from the EHR, particularly on a scale broader than a single institution. It was noted that Epic plans to use Cosmos, a data warehouse that includes a version of Epic's analytics toolset (Slicer-Dicer) that researchers can use to explore the data, to integrate into PatientsLikeMe (an integrated community, health management, and real-world data platform) that contains over 850,000 members and over 2900 disease conditions. A vendor panel convened by NHGRI could provide more insight regarding how to supplement these genomic-based repositories with phenotype information.

It is also essential to consider how a patient moves through the healthcare system. Regarding the smart contracts in which patients decide what data they would and would not like shared with themselves or others, these should be amendable such that a patient can change their preferences regarding data access to their information. It would also be ideal for health care providers to track a patient's care from pediatric to adult to old age with the genomic data moving with the patient through the health ecosystem. Some EHR vendors are beginning to explore this by working with cloud vendors. This capability could allow data to be stored and made accessible to and from various institutions. Still, it is important to ensure that only those the patient has agreed to through the contract can access the data. Research into recontact, particularly in the absence of provider oversight, would be helpful here. Addressing sociological barriers to network ecosystems is also crucial for this. NHGRI-supported implementation science research and other alternative models would help empower patients. Understanding the knowledge needed by patients to utilize this patient-centric approach is necessary.

Session 3: Researching The Stakeholder Perspective: Enablers and barriers that affect the integration of genomic-based clinical informatics resources in the health care system

Both point-of-care and population-based CDS systems are critical resources in the healthcare system. However, most studies around CDS tools focus on point-of-care tools. An emerging standard in point-of-care tools is CDS Hooks, which pushes an alert to the clinician based on interaction with the EHR (e.g., prescription of medication, pre-and post-genetic test). These CDS tools work on the backend of health care systems allowing an algorithm to scan EHRs for patient records to identify whether the patient meets specific criteria and direct the clinician through established workflows to the appropriate point-of-care tools. This process also includes point-of-care standards such as Infobutton and SMART on FHIR for test interpretation and guidance for these workflows to function correctly.

However, the current standards and processes used to establish CDS systems are not conducive for gCDS tools. The most pressing research gaps in the development and implementation of gCDS tools include leveraging existing standards and developing novel workflows that diminish burdens for primary care providers, tap into other healthcare workers and engage patients beyond standard approaches such as alerts and reminders. Research needs to embrace a strategy of

reduction of socio-technical challenges. This objective will require increased research on human factors, user interface, and workflows. There must be continued investment in informatics research for genomic evidence computing and genomic knowledgebase construction to enable scalable, sharable, and computable inferences of genomic knowledge and harmonization of practice guidelines. The field must harmonize multiple stakeholders' interests and forge new collaborations to develop a learning healthcare system for genomics. However, most generalists and specialists do not consider or use gCDS tools when they are made available. Critical barriers to clinician use of gCDS tools include lack of support from hospitals, lack of current knowledge to practice evidence-based genomic medicine, and poor EHR user interface and integration. Nonetheless, EHR-based informatics research results and implementation science, along with FHIR standards, are enabling clinicians to overcome those barriers. However, there must be continued investment in informatics research for genomic evidence computing and genomic knowledgebase construction to allow scalable, sharable, and computable inferences of genomic knowledge and harmonization of practice guidelines. The field must harmonize multiple stakeholders' interests and forge new collaborations to develop a learning health system for genomics.

FHIR has a lot of promise and potential as a method for exchanging healthcare information electronically, but it is still relatively early in its implementation. Content standards around variant interpretation are still limited. Pressingly, there is a strong reluctance in health systems to use third-party operating systems in production systems. And although labs are willing to pay for third-party niche applications, providers are much less inclined to pay for EHR-adjacent gCDS tools.

The best way to address these challenges is to provide funding to train providers and develop standards to support genomic medicine. Demonstrating the financial benefits of using genomic information to improve care can encourage adoption on the administrative end. Research into the economic benefit of doing genomic analysis can reveal the cost-effectiveness for both the health system and patient. The value proposition of clinical informatics systems may ultimately be the deciding factor in the widespread adoption of gCDS tools.

Discussion

Data security is critical to interoperable health systems' function; however, data security requirements can be frustrating to work with and counterproductive if security concerns override the need to use patient care information. Optimizing data security among all parties will require early engagement with the security team and treating them as partners rather than adversaries.

Another way to familiarize clinicians with genomic medicine is with medical training. Among other benefits, this may help clinical teams diagnose undiagnosed diseases early instead of using sequencing and genomic medicine as a last resort (after spending tens of thousands of dollars).

At present, genomics is intimidating to many providers. Pharmacogenomics and rare disease diagnosis may be the most accessible entrée point. Even without the extra training, it may help ensure that the EHR alerts' language is in an accessible format for clinicians without genomics training to use.

Although ideally, all clinical centers will be able to integrate gCDS tools with their EHR, that is not currently a reality for many small community health centers. For example, genomic medicine will not be anywhere near the top of the priority list for a health center that struggles to do routine colorectal cancer screenings.

Ideally, the EHR would be constantly updated with new, clinically relevant findings. However,

most of these findings are represented in a PDF format, wherein the data are inaccessible without text-mining systems. There is also a lack of policy clarity around the reuse of sequencing data. Sequencing is presently done under a lab pathology model. Would reinterpretation of that data be eligible for reimbursement?

This topic could be a good candidate for NHGRI support. Other candidates include research into EHR models that 1) do not rely on primary care providers to do extra work and 2) engage the patients (e.g., patient portals or smart devices). NHGRI could also support the research and development of standards-based, computable, evidence-based infrastructure for clinicians along with interoperable knowledgebases. Metrics of success in this area remain to be defined and are probably diverse but will likely be determined by patient outcomes. A research agenda into the policy and regulation that impacts this area was also suggested.

Session 4: Defining A Research Agenda That Addresses The Process For Developing Genomic-Based Clinical Informatics Resources

Health information technology (IT) plays a critical role in research. The Office of the National Coordinator for Health Information Technology (ONC) is at the intersection of research and care delivery. ONC promotes and leads activities that spur innovation, support patient-centered outcomes research, and advance precision medicine. The ONC's Policy and Development Agenda articulated a vision of health IT infrastructure to support alignment between clinical and research ecosystems to improve research's speed and effectiveness. This agenda's goals are to leverage high-quality electronic health data for research and advance health IT infrastructure to support research. One concept that is emerging and worthy of research consideration is how to learn from less data. Other ONC projects include the Precision Medicine Initiative (PMI) and Sync for Genes. The PMI is a nationwide initiative to deliver care to patients as individuals by supporting health IT interoperability for research and adopting and advancing standards for privacy and security of data and participant-driven data contribution. Sync for Genes aims to standardize genomic information sharing between laboratories, providers, patients, and researchers. Another resource advocated by ONC and should be considered for research supported by the NHGRI is The U.S. Core Data for Interoperability (USCDI), a set of health data classes and constituent data elements used for a nationwide interoperable health information exchange. The USCDI draft version 2 was recently released but lacked representation for genetics and genomics-related information. Since the USCDI is updated annually, the NHGRI could provide guidance to address this gap. NHGRI should be also be encouraged to collaborate with ONC to help foster the development and advancement of genomics into health IT infrastructure. Such a collaboration would provide an efficient link of research findings to policy implementation that would benefit the broad genomic-focused healthcare community.

Genomic-based clinical informatics resources can support precision oncology and evidence curation. For example, the Pancreatic Cancer Action Network's Know Your Tumor program is an AI-based virtual molecular tumor board (VMTB). This VMTB was engineered by collecting, extracting, and structuring over four years of published data, combined with patient-specific information. The goal is to utilize the collaborative, multidisciplinary evaluation of cancer variants through VMTBs to inform local clinical practices. Barriers to this include a high level of manual curation and data integration, a need for variant interpretation consensus, a demanding number of knowledgebases, a lack of resources, and a need for uptake by clinical researchers. Another example of a Natural Language Processing pipeline to automatically extract clinical genomic evidence for variant interpretation uses the concept of learning from less data. Research

should address ways to reduce reliance on manual curation processes. There is a need for common data models for “semantic extraction,” understanding that there are multiple ways to represent the same idea.

Integration of genomic data into the EHR is an ongoing process with challenges presented by the various EHR vendors employed among institutions and the fact that the majority of genetic data remains in PDFs. The major EHR vendors approach the integration of genetic data in different ways and offer an opportunity to explore different techniques for genomic data integration efforts. There is another challenge in the difference of needs for clinical geneticists compared with primary care providers. This challenge can be addressed by defining separate but compatible workflows for different genomics use cases. EHR vendors also follow two different standards – Health Level Seven (HL7) v2.5 and FHIR. Laboratory information systems (LIS) do not support either standard, so research should work on interfaces between the LIS and the EHR. Other challenges include maintenance of clinical information and decision support as well as classification and reclassification of variants. Once these challenges are overcome, the EHR containing genomic data will facilitate real-time use of the entire sequence in patient care. Risk analysis research is a valuable next step to address any “regulatory nightmare” that will impact the use of the whole sequence in clinical care.

Discussion

Common data models should drive research in this area, but these are currently lacking. Since the EHR only recently provided structure with improving HL7 standards, there is an opportunity for widespread adoption of a common data model. The USCDI offers an opportunity to incorporate more specificity. Implementation science research should be funded. Additionally, it is crucial to identify the user needs. NHGRI should identify the relevant stakeholder groups and their needs, particularly ensuring the inclusion of patients.

A responsibility model would determine who is accountable for ensuring that information reaches the patient. This model needs to be developed to ensure that the healthcare system delivers timely results in a proactive and preventive manner. Suppose the patient receives a result relevant to a disease in a different clinical area than the one in which the test was ordered. In that case, a responsibility model will ensure that this result would reach a provider who can implement the appropriate care for said patient.

Research at the interface between humans and AI is also of interest for developing genomic-based clinical informatics resources. Research in other fields has demonstrated that combining AI with a physician outperforms either entity on its own. Innovative collaborations between different stakeholders are needed to advance standards for participant-driven research.

Session 5: Genomics In A Fragmented Healthcare Environment

In the past, clinicians have traditionally used genetic information to treat a patient when that patient presents with a problem. Now, genomic medicine is moving toward a model in which the patient shows up with genetic information in hand. Clinicians’ strategies are also evolving; they can now develop prevention strategies based on patient's genetic test results and develop treatments based on the same information. On a broader scale, healthcare systems can identify patients who are “at-risk” for follow-up, deeper evaluation, and phenotyping. Healthcare systems can also identify patients for genotype-guided clinical trials and return information to patients about their genetic risk. However, to fully adopt this new paradigm, clinicians must access sequence information across a patient’s lifetime. This process should include information such as

Mendelian disease risk genes, pharmacogenomics, and polygenic risk scores. For example, testing for one condition might return another pathogenic result that is not relevant for the testing indication and is not returned to the patient. This information must be available to the EHR with accessibility to both the patient and provider when it becomes relevant. EHR systems are starting to build capacity for storing genetic information as structured data. With gCDS built to disseminate the relevant genomic sequence information, healthcare providers across the system can find and use the information. As patients move among health systems, Health Information Exchanges (HIE) can share relevant genetic information. This capability is theoretical at present. As more progress is made in genomic medicine, informatics systems can push annotation updates to patient records based on the stored genomic sequence data.

Before this model is fully implemented, gCDS tools need to include individual genomic indicators and must be subject to regular updates. Additionally, providers across the system need more education around genomic medicine and EHR systems. For their part, the gCDS tools need infrastructure to alert providers appropriately without overwhelming them with excessive or irrelevant notifications. On the HIE end, genetic data sharing does not always happen as it is supposed to, and many providers are unfamiliar with the system.

Since knowledge about genome function changes regularly, there is a need to update annotations and interpretations. Those annotations also lack widely implemented standards, and broad ontology adoption is lacking. Cloud-based resources can assist in providing a scalable infrastructure for HIE. But research to mitigate cloud user-associated costs (e.g., storage costs and egress) is needed to prevent exacerbating health disparities.

Why is there no broad clinical genetic exchange? What must be done to ensure that it will improve rather than reduce health equity once such an exchange exists? These are big questions in clinical informatics. In a perfect world, all clinical labs would send structured genetic reports that could route to providers and patient records, where they could then be integrated with other clinical data. These EHRs would also be routinely updated with new genetic information and guidelines. In reality, all the current clinical genetic exchanges are small because they are expensive to build and maintain. The only way to fund these systems is for institutions to decide to invest their own money in the designs. For institutional stakeholders to make that investment, the system must clear three hurdles: technical feasibility, clinical benefit, and financial viability. Then, it can be considered for prioritization relative to potentially hundreds of other needs.

The value propositions for clinical genetic laboratories, research programs, and knowledge repositories are clear. Genetic exchanges will strengthen test values, distribution, the impact for the laboratories and research programs, and repositories. For hospitals, the value proposition is less clear. Genetic exchange can fundamentally accelerate the rate and improvement of care. However, financial viability is the biggest hurdle. Not only must the genetic exchange show clinical benefit to specific patients, but adoption is often only feasible if there is a source of revenue or savings immediately following adoption. Initial costs include assigning clinical IT personnel, working with vendors, paying for integration, updating clinical workflows training, and validating the new processes. On an ongoing basis, hospitals will also have to pay to maintain integration and quality over time. Still, there are many potential hospital value levers. A robust genetic exchange system may aid in the patient acquisition, service line expansion, and quality improvement. It may also reduce the risk of liability and burnout.

Research into the establishment and implementation of genetic exchange systems can engage hospital decision-makers to determine what applications or value propositions could trigger grant-independent institutional investment in genetic information technology infrastructure.

These decision-makers would include the Chief Executive, Financial, Operating, Medical, and Information Officers of large, medium, and small institutions. Systems developers could fund projects to produce applications that spark this institutional investment.

Research can also study the economic dynamics of genetic IT infrastructure projects. After cataloging both value creation and cost reduction opportunities, developers could focus standards funding on reducing costs and increasing the value of implementing the highest value applications.

Genetic exchange is a specific example of interoperability in genomic medicine. Interoperability requires normalized datasets for analysis and discovery but can also lead to optimization of patient- and population-level care.

FHIR is an emerging specification used to exchange healthcare information electronically. It is gaining rapid industry adoption and has been endorsed by the NIH. As required by USCDI regulation, HL7 has an FHIR US Core Implementation Guide Version 3 (IG³). However, there are several versions and several implementation guides for FHIR.

SMART on FHIR allows the embedding of third-party applications in the EHR and has widespread vendor support. It supports patient-facing apps (e.g., Apple Health). In some cases, SMART may augment the EHR FHIR server to add needed data or filter out unnecessary data. SMART also uses OAuth 2 to delegate users' data rights to the app.

SMART uses FHIR to read (and sometimes write) data and use Clinical Quality Language (CQL) and CDS Hooks for logic evaluation. CDS Hooks has been a standard since 2019, and its userbase is growing. It is a companion standard to SMART on FHIR. CQL has been a standard since 2015 and enjoys widespread use. It enables the expression of computable phenotypes, decision support logic, and clinical quality measures.

The University of Utah's "Reimagine EHR" program is a multi-stakeholder initiative that started in 2016 to leverage FHIR and related standards. It was an early leader spanning research and operations with its agile, collaborative, and innovative environment. Its steering committee, co-chaired by the Chief Information and Medical Information Officers, oversees more than \$300 million in grants. Its solutions to problems of interoperability and accessibility include personalized medicine for lung cancer and diabetes through SMART on FHIR. The diabetes tool uses AI-driven prescription drug guidance combined with individuals' insurance coverage to help clinicians choose their patients' best options. Despite the utility of FHIR, per-patient FHIR access approaches are too slow for population-level data retrieval. FHIR Bulk Data Access (Flat FHIR), currently in development, could address this issue. Researchers could leverage and normalize large datasets retrieved through Flat FHIR. Another facet of "Reimagine EHR" is a FHIR-based population health management effort that aims to identify and manage individuals at elevated risk of breast or colorectal cancer. Approximately 13% of people are at elevated risk for developing these cancers, but most are unaware of it. An AI is used to extract data from free text, and then patients can be contacted and educated via chatbot. Although there have been impressive advances in the field, challenging problems largely persist for FHIR. Critical challenges to full FHIR implementation include data normalization, execution performance, and the "last mile" of translating FHIR standards into practice. Furthermore, EHR vendors must offer support and standardization beyond the basics. For example, they must support detailed clinical models, genomics support, and population-based health management approaches. The clinical informatics field must coordinate and synergize with the broader health IT community to accelerate the necessary developments listed above and facilitate the entire transition lifecycle, including that "last mile" of clinical implementation.

Discussion

At the moment, there is not a robust exchange of genomic-based health information. The focus is on ensuring that providers interested in using genetic data know how to use it; there is no interest in pushing out genetic information to clinicians who do not want it. The standardization of dynamic genome annotation and interpretation should be a high priority on the research agenda. Another high priority should be building the infrastructure to support and integrate these functions into the EHR. On the clinical research side, NHGRI can support the research agenda by producing use case-based evidence to show that genetic interoperability is the right way to care for patients. These use cases would direct the clinical informatics community toward the best places to invest resources. Another important aspect is to demonstrate that genetic interoperability is both scalable and economically viable. On the discovery side, NHGRI can support the use of FHIR in the efforts to map lab components to link codes. Other places where NHGRI support would be valuable include revamping the “innovation” component of grant review. It is challenging to write grants to make small changes to FHIR, as those minor tweaks are rarely considered innovative enough for funding. NHGRI can also help bring together a variety of stakeholders. Engaging with executives, research scientists, clinicians, IT professionals, and other knowledgeable people in the field who know the case studies across multiple institutes would broaden perspectives of where to see the best return on investment. Legal and bioethical expertise will also be valuable in implementing new services and maximizing return. At present, clinical informatics does not have the pipeline needed to increase diversity and equity. More research is required to design equitable workflows and make services available to minority and underserved communities. Clinical informatics needs to reach people where they are and push genetics and genomics in languages users can understand and use. Finally, there may already be great ideas for increasing diversity in clinical informatics around the country that have already been implemented to great success. It may be for the entire field's betterment to replicate successes already in place instead of trying to reinvent the wheel.

Session 6: A Genomic-Based Informatics Research Strategy

Overarching themes for developing a research strategy on using genomic-based clinical informatics resources to improve the detection, treatment, and reporting of genetic disorders in clinical settings were identified and discussed. Research should include an implementation science framework with clarity regarding the definition of implementation science. NHGRI should support multi-stakeholder collaborations because patients, research participants, providers, payers, C-suite, researchers, and the private sector all have a value proposition. In developing apps to promote genomic medicine under patient control, the patients need to be engaged. Pervasive detrimental bias in data, information systems, access, value, and knowledge must be recognized and addressed. Research must account for relevant workflows, but it may also need to facilitate workflows to include new aspects that incorporate genomic data. Researchers should develop and utilize core outcome measures to demonstrate the value of genomic-based informatics. Finally, research should also be aimed toward enabling learning health systems.

Critical needs identified from the survey are for research into methods for integrating analytical interpretations derived by computational models of genomic data into clinical settings. These methods also include ways to ensure that CDS can incorporate and support multiple genes and clinical information. Research efforts in this space need to consider preferences in content and workflow across a broad range of stakeholders. There should also be research into the impact of

policy and regulation on implementing Genomic Informatic strategies. Finally, there is a need to study models to support the sustainability of such strategies.

The major themes from each session were also identified and discussed. From Session 1, it was noted that detrimental biases in data, algorithms, information systems, and implementation must be studied and addressed rigorously and systematically. These biases must be evaluated as having multidimensional components and should include race/ethnicity, social determinants of health, urban/rural, academic vs. non-academic centers, and implementation equity.

Implementation equity will require outreach to organizations typically not included in this type of research to actively solicit their input and participation. Additionally, there is a need to explore the value proposition that is imbalanced between researchers and participants. Outcomes must capture both benefits and harms of gCDS to inform mitigation approaches.

Session 2 highlighted the need to use implementation science research methods to improve implementation equity. The research agenda should be patient-centered and address privacy and security of data, recontact of patients, and approaches to reduce bias. To attract a broad range of stakeholders, research needs and should be leveraged to provide meaningful use to update the current “business model” used to evaluate a tool or resource's utility. Research should focus on representing genomic information as structured data to minimize efforts in using manual processes for curation. Finally, research should identify methods to “close the loop” to reuse genetic data that moves through health systems with the patient.

The presentations and discussion during Session 3 identified the need for informatics research for genomic evidence computing and genomic knowledgebase construction to enable scalable, sharable, and computable inferences of genomic knowledge and harmonization of practice guidelines. There should also be research into novel workflows that diminish burdens for providers and engage patients. Studies should ensure that new technologies do not exacerbate health disparities but also work to reduce them. Educational and policy research should reduce barriers and improve knowledge for patients and providers.

From Session 4, research should focus on what constitutes the minimum data for clinical care as well as how to “learn from less data.” There should also be research that focuses on improving the interface of human cognition and AI and explainable AI to promote implementation.

Research should investigate the development and implementation of a responsibility model across the EHR for patient access to information. Additionally, research should investigate how modifying the regulatory frameworks can facilitate the development and implementation of genomic-based clinical informatics tools and resources while improving clinical care. New technologies such as tele-genomics should also be considered for outreach, consultation, and delivery of results.

Session 5 identified the need for research into data interoperability between clinical systems focused on implementing genomic medicine. There should also be research on specific use cases to support genomic medicine implementation through informatics. These use-cases should be prioritized based on diverse stakeholders, and some should involve the reuse of genomic information. NHGRI should coordinate and synergize research findings with the broader health IT community. NHGRI should also facilitate the “last mile” of clinical implementation by identifying what has been developed and supporting implementation science research. Finally, data should be made accessible to the basic research community.

In conclusion, each of the recommendations mentioned in this summary also addresses key concepts described in the NHGRI's recently published “Strategic vision for improving human health at The Forefront of Genomics.” For example, topics covered in this workshop addressed

investing in implementation sciences, collecting outcomes for use to improve the business model of advanced technologies, and research in developing and enacting genomic-based clinical informatics tools and resource strategy. These fit well into the areas of emphasis, described in the NHGRI strategic vision, particularly those needed to develop a sustainable genomic learning healthcare system. Also, recommendations related to addressing the inclusion of broad and diverse stakeholders when developing tools and resources and studying the intersection of AI and human cognition are ideal examples of key components described in the strategic vision needed to provide a sustainable and improving robust foundation for genomics.

Summary and Next Steps

The Executive Summary details the lessons learned and recommendations from the meeting. All of the presentations and video recordings from the meeting can be accessed on the GM XIII [website](#). In addition to this Meeting Summary, co-chairs Drs. Ken Wiley and Marc Williams will be working to develop a manuscript for publication that is based on the outcomes from this meeting. Speakers and moderators are encouraged to contribute as co-authors.

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