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Research and Applications

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A research agenda to support the development and implementation of genomics-based clinical informatics tools and resources

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ABSTRACT

Objective: The Genomic Medicine Working Group of the National Advisory Council for Human Genome Research virtually hosted its 13th genomic medicine meeting titled "Developing a Clinical Genomic Informatics Research Agenda". The meeting's goal was to articulate a research strategy to develop Genomics-based Clinical Informatics Tools and Resources (GCIT) to improve the detection, treatment, and reporting of genetic disorders in clinical settings.

Materials and Methods: Experts from government agencies, the private sector, and academia in genomic medicine and clinical informatics were invited to address the meeting's goals. Invitees were also asked to complete a survey to assess important considerations needed to develop a genomic-based clinical informatics research strategy.

Results: Outcomes from the meeting included identifying short-term research needs, such as designing and implementing standards-based interfaces between laboratory information systems and electronic health records, as well as long-term projects, such as identifying and addressing barriers related to the establishment and implementation of genomic data exchange systems that, in turn, the research community could help address.

Discussion: Discussions centered on identifying gaps and barriers that impede the use of GCIT in genomic medicine. Emergent themes from the meeting included developing an implementation science framework, defining a value proposition for all stakeholders, fostering engagement with patients and partners to develop applications under patient control, promoting the use of relevant clinical workflows in research, and lowering related barriers to regulatory processes. Another key theme was recognizing pervasive biases in data and information systems, algorithms, access, value, and knowledge repositories and identifying ways to resolve them.

Key words: genomics, clinical informatics, clinical decision support systems

INTRODUCTION

The use of genomics in clinical care has advanced our understanding of the etiology of disease and is leading to improvements in diagnostic screening, disease prevention, and treatment. However, after years of exciting genomic discoveries relevant to clinical care, there remain barriers that healthcare providers face when trying to integrate genomics-based data into both the electronic health record (EHR) and clinical decision support systems (CDSS). Optimal characteristics of genomic information were initially described in the Technical Desiderata for integrating genomic data into EHRs and CDSS.[1,2] The National Human Genome Research Institute (NHGRI) has aimed to identify and prioritize these barriers and stimulate research efforts to resolve them through a series of workshops and related activities. For example, NHGRI's recently published 2020 strategic vision for the future of genomics includes key elements for sustaining and improving a robust foundation for genomics.[3] These key elements were generated from input from over 50 meetings and events. One key element described in this 2020 strategic vision is the need to invest in research that focuses on improving the accessibility and usability of genomic information for clinicians through CDSS and other tools.

Recognizing the importance of integrating genomic information into EHRs as a significant issue predates the 2020 NHGRI strategic vision. The Genomic Medicine Working Group (GMWG), a working group of the National Advisory Council for Human Genome Research, focused its 2014 genomic medicine meeting on "Genomic Clinical Decision Support—Developing Solutions for Clinical and Research Implementation" (GMVII).[4] This meeting involved key thought leaders in genomic medicine implementation and genomic clinical decision support (CDS) to define gaps and develop strategies to resolve them. The GMVII meeting also focused on identifying and engaging health information technology initiatives to support recommended strategies and define and prioritize a genomic CDS implementation research agenda. Informed by the GMVII meeting and the 2020 NHGRI strategic vision, the GMWG organized its 13th genomic medicine meeting (GMXIII) titled "Genomic Medicine XIII: Developing a Clinical Genomic Informatics Research Agenda". The goal of GMXIII was to develop a research strategy to reduce barriers for the genomics community in developing and using Genomics-based Clinical Informatics Tools and Resources (GCIT) to improve the detection, treatment, and reporting of genetic disorders in clinical settings.

The specific objectives of the meeting included:

- Define the status of GCIT and related knowledge gaps,
- Determine facilitators and barriers that affect the development and deployment of GCIT research needed to support the former while also resolving the latter, and
- Identify research needed to improve how GCIT affect the patients and clinician decision-making processes.

This article describes progress in the field from 2014 to 2021, highlights available GCIT for improving preventive and therapeutic care, discusses the key themes from the meeting emphasizing progress while identifying new and remaining challenges, and describes how NHGRI and the scientific community can promote research in GCIT.

METHODS

The speakers and moderators were invited by a GMXIII planning committee and the GMWG based on their content expertise. The participants included experts in genomic medicine, clinical informatics, clinical medicine, research, and health policy as well as representatives from the National Institutes of Health. Each session also included a moderated discussion component to allow attendees to share their experiences and to identify and prioritize barriers that

NHGRI should consider in their plans to stimulate research in GCIT. The meeting was recorded (https://youtu.be/DUp7JLeL8iM) and dedicated note-takers summarized the sessions. After the meeting, presentations and associated discussions were reviewed by the planning committee, the GMWG, and NHGRI staff to identify key themes and create a meeting summary (https://www.genome.gov/event-calendar/genomic-medicine-xiii-developing-a-clinical-genomic-informatics-research-agenda). The summary was reviewed, edited, and approved by all speakers, moderators, and the GMWG and NHGRI staff.[5]

In advance of the meeting, a survey was circulated to invitees to gather feedback on progress made in addressing the elements that are described in the "Technical Desiderata for the Integration of Genomic Data into Electronic Health Records"[2] and the "Technical Desiderata for the Integration of Genomic Data with Clinical Decision Support"[1] (Supplemental Table S1a). To reflect the changes in the genomics and informatics landscapes since these publications and to support the collection of information relevant to the objectives of the meeting, the planning committee considered developing additional questions. Eight additional questions were included in the survey and were vetted by the GMWG and NHGRI staff (Supplemental Table S1b). Respondents were asked to rate the importance of the elements of the Technical Desiderata using a 5-point Likert scale (1—strongly agree to 5—strongly disagree). A "don't know" response option was also provided. The survey responses were collected using Qualtrics®. The mean and standard deviation of the responses were obtained. Respondents also had the opportunity to rank the importance of the 14 desiderata elements and provide free-text responses on barriers and gaps involving the development and implementation of GCIT. The planning committee reviewed these surveys to identify points to guide discussion for the GMXIII workshop. Before the meeting, narrative comments relevant to specific content areas were provided to speakers for incorporation into their presentations. Finally, the GMXIII meeting was divided into 6 sessions, and the review group identified priority themes from each session (Table 1).

RESULTS

One hundred fifty individuals attended the GMXIII meeting, including 2 co-chairs, 16 speakers, and 10 moderators. A full meeting report can be found on the GMXIII meeting site.[5] Surveys were sent to 83 early registrants, all invited speakers, and moderators. Thirty-three participants provided a response (39.8% response rate), and all who started the survey completed all questions. The key findings (unprioritized) from the survey include the following:

- The genomic medicine community can benefit from a revised Technical Desiderata document;
- Current methods for storing genomic and genomics-based information are not adequate to allow CDSS to incorporate and support multiple genes and associated clinical information;
- Methods related to ontology management and knowledge representation for genomics-based clinical interpretation have not been adequately addressed by the research community;
- Methods for integrating analytical interpretations derived by computational models of genomic data into clinical settings are not well established;
- Methods for evaluating the clinical utility of GCIT are fluid and not well defined for the research community to use in their research and development plans; and
- The genomic medicine community has not adequately addressed efforts to modify clinical workflows to reduce instances of "alert fatigue".

Results from the survey and a copy of the survey questions can be found in the Supplemental Materials. Prioritization of the desiderata had also been assessed in GMVII, which had 25 out of 35 attendees (83% response rate) complete a similar survey to that used in GMXIII. The results of the priority ranking from the 2 surveys conducted 7 years apart are shown in Table 2. Two items were high priorities at both meetings: "CDS knowledge must have the potential to incorporate multiple genes and clinical information" and "CDS knowledge must have the capacity to support multiple EHR platforms with various data representations with minimal modification." However, several items showed significant changes in priority between the 2 meetings. Three items—"Leverage current and developing CDS and genomics standards," "Maintain linkage of molecular observations to the laboratory methods used to generate them," and "Maintain separation of primary molecular observations from the clinical interpretations of those data"—had relatively low priority in GMVII but had a higher priority in GMXIII. In contrast, "Support a CDS knowledge base deployed at, and developed by multiple independent organizations" and "Simultaneously support human-viewable formats and machine-readable formats to facilitate implementation of decision support rules" were given a relatively low priority in GMXIII compared to GMVII. Many respondents provided free-text responses (Supplemental Materials). Analysis of the responses identified 4 additional elements not represented in the desiderata:

- Importance of assessing stakeholder preference and workflow;
- Sustainability of resources;
- Lack of methods for evaluation of innovation and implementation of GCIT tools; and
- Impact of the consent and regulatory framework.

DISCUSSION

The outcomes of GMXIII make a strong case for developing an informatics implementation research agenda to focus on improving how GCIT impacts patients and the clinical decision-making processes. The ability to compare priorities, barriers, and facilitators across the 7 years between GMVII and GMXIII was particularly useful in defining elements of a research agenda, even though the foci of the 2 meetings were somewhat different. While some progress has been made, many of the barriers identified in the 2014 GMVII meeting are still present in 2021. The top priority issue from both the surveys is the need to incorporate multiple genes and related clinical information into CDS systems that are integrated into EHRs. This priority was also reinforced in free-text comments reflecting the desire by more groups to implement genomic medicine in the clinic. Elements that maintained the same ranking in both the GMVII and GMXIII meetings suggest a need for a patient-centered research agenda to develop innovative platforms for obtaining and returning genetic tests. Elements that received higher priorities in the GMXIII survey, compared to GMVII survey, also highlight a need for researchers to engage across a broader range of organizations to work collaboratively in addressing these elements. Consistent with this, the use of existing or developing standards for both genomic data and CDS moved to a higher priority in the 2021 GMXIII survey compared to the 2014 GMVII survey responses. These results

Table 1. GMXIII title sessions, objectives, and recommendations

Session title	Objective	Attendees' recommendations to address objectives
Making the case for a clinical genomic informatics research strategy	Highlight the current state of GCIT efforts in reducing barriers to implementing and advancing genomic medicine.	• Identify elements from the survey and the Technical Desiderata where significant progress has been made and identify those that require additional engagement; • Ensure that the development and implementation of GCIT is done in a manner that includes equitable representation from diverse and underserved populations; • Ensure innovative research questions and methods address inherent biases in a rigorous and systemic manner; • Report outcomes from GCIT efforts that capture outcome data on both the benefits and harms of GCIT in their use in CDS to improve mitigation approaches.
Need for research in advanced technologies (AT) to support Genomic Medicine	Identify areas that need support in the development and implementation of AT to advance genomic medicine, including technology for improving genomic medicine implementation in healthcare delivery both within and outside of the traditional patient visit.	• Invest in research that advances a patient-centered approach in the development and implementation of AT; • Ensure that research in AT conducted by the genomics research community complements efforts in the private sector; • Support research that generates outcomes that can be used to inform the business model of AT in a manner that attracts a broad range of stakeholders in understanding more about the incentives to implement these tools and resources.

Researching the stakeholder perspective: enablers and barriers that affect the integration of genomics-based clinical informatics resources in the healthcare system	Describe the necessary partnerships, collaborations, and processes needed to generate a sustainable GCIT research strategy.	• Incentivize collaborations in the development, implementation, and maintenance of a learning healthcare system for genomic medicine;
		• Incorporate educational and policy research components that focus on reducing barriers and improving knowledge for patients and providers;
		• Focus on the development, implementation, and maintenance of genomics-based workflows that:
		  • Diminish burdens for primary care and specialty providers;
		  • Involve the full health care team and engage patients;
		  • Go beyond alerts and reminders to disseminate meaningful information for CDS.

Defining a research agenda that addresses the process for developing genomics-based clinical informatics resources	Explore the role health information technologies play in advancing research in genomic medicine.	• Focus on the interface of human cognition and artificial intelligence to leverage the best of both approaches to improve patient care; • Lower the regulatory barriers for the development and implementation of GCIT without compromising patient safety; • Develop and implement a common semantic framework that enables interoperability and reduces reliance on manual curation.
Genomics in a fragmented healthcare environment	GCIT's quality improvement strategies, genomic medicine practice innovations, outcomes data collection, and analysis.	• Invest in the development of specific use cases that support genomic medicine implementation through informatics; • Invest in research that focuses on establishing a genomics-based health information exchange system in a manner that synergizes with the broader health information technology community's efforts in this space; • Support efforts that facilitate not only the development of GCIT but also the "last mile" of clinical implementation into healthcare systems.

Table 2. GMVII and GMXIII Technical Desiderata elements ranking for the integration of genomic data into electronic health records and clinical decision support

Technical Desiderata elements	GMVII Ranking, 2014	GMXIII Ranking, 2021	Ranking changes over 7 years
Maintain separation of primary molecular observations from the clinical interpretations of those data	11	3	+8
Maintain linkage of molecular observations to the laboratory methods used to generate them	7	2	+5
Support lossless data compression from primary molecular observations to clinically manageable subsets	12	6	+6
Leverage current and developing CDS and genomics standards	8	4	+4
Keep CDS knowledge separate from variant classification	13	11	+2
Support a large number of gene variants while simplifying the CDS knowledge to the extent possible	9	7	+2
CDS knowledge must have the potential to incorporate multiple genes and clinical information	1	1	=
CDS knowledge must have the capacity to support multiple EHR platforms with various data representations with minimal modification	5	5	=
Access and transmit only the genomics information necessary for CDS	14	14	=
Support a CDS knowledge base deployed at and developed by multiple independent organizations	4	12	−8
Simultaneously support human-viewable formats and machine-readable formats in order to facilitate implementation of decision support rules	3	10	−7
Support both individual clinical care and discovery science	2	8	−6
Support compact representation of clinically actionable subsets for optimal performance	6	9	−3
Anticipate fundamental changes in the understanding of human molecular variation	10	13	−3

Note: = element received a higher ranking in the GMXIII survey than the GMVII survey. = element received a lower ranking in the GMXIII survey than the GMVII survey.

could be indicative of survey respondents' biases. However, the results could also be attributed to the recent emergence of genomic data standards, such as those developed by the Global Alliance for Genomics & Health (GA4GH), the genomic standards consortium, and the Health Level Seven's Fast Healthcare Interoperability Resources® (FHIR®). Two items—CDS knowledge base and support for human and machine-readable CDS—had much lower priority based on the 2021 GMXIII survey response than the 2014 GMVII survey response, possibly because progress has been made.[6,7] However, research opportunities in these areas are still present.

Several new priorities were identified from the meetings that were not described in the 2 surveys. Prioritization of issues such as stakeholder engagement, workflow assessment, measurement of effectiveness and outcomes of implemented systems, development of educational and support materials, regulatory and policy analysis, and assessment of equity for diverse and underrepresented communities indicate that more attention is being directed towards issues critical to the implementation of genomic medicine. These priorities have significant implications for any research agenda. Specifically, the incorporation of expanded research methods emerged as an important overarching theme. Examples include using methods and models from various disciplines, including implementation science, user-centered engagement and design, business case analysis, and workflow analysis.

Equity and inclusion were recurring themes that arose in many of the sessions. Clinical genomics research, including related informatics tools and resources, must acknowledge how race, ethnicity, ancestry, gender, and other social determinants of health impact genomic medicine and clinical implementation of genomic information. For example, Black and Hispanic patients are less likely than White patients to be referred to or included by default into screening programs based on observed genetic risk, even after adjusting for disease-specific population allele frequencies.[8,9] Total medical expenditures per capita are roughly similar between Black and White populations even though Black populations are sicker.[10,11] GCIT research methods must include ways to identify and mitigate inherent and pervasive biases impacting data, knowledge, infrastructure support in EHR systems, access, and value definitions that interfere with the meaningful and beneficial use of genomics in clinical care. Genomic medicine specialists must be antiracist and proactively seek to identify and remove harmful biases that affect data and systems used for research and clinical care. GCIT need to include education, training, and policy components that reduce barriers and improve knowledge for patients and providers. The goal of clinical informatics and EHR integration of genomics and related information should be to support research that proactively and explicitly improves outcomes, avoids increasing clinicians' workloads, and addresses systemic biases in data, information systems, and clinical care delivery.

Attendees strongly supported substantive stakeholder engagement at all points of GCIT in languages that users can understand and employ to reduce barriers in improving knowledge for patients and providers. Efforts to develop GCIT must include individuals from diverse backgrounds and experiences, monitoring for bias and discrimination at different stages of development and implementation, establishing robust equity policies, and having developers work with patient engagement groups before, during, and after any GCIT initiative. Research based on clinically meaningful use cases as defined by patients, clinicians, and other stakeholders is essential to attain these research objectives. GCIT research needs to note the importance of engaging with diverse institutions with intentional outreach to institutions and delivery systems not typically represented in informatics and genomics research to address the lack of diversity at the institutional level and improve the generalizability of results.

Table 3. Short-term projects (1–3 year timeline)

Developing new and modifying existing tools and workflows to address systemic bias in genomics-based data and information systems used in health IT
Revising the Technical Desiderata
Developing user-friendly clinician- and patient-centered genomics-based tools and workflows
Identifying and addressing semantic and syntactic gaps related to the representation of genomic information in existing clinical data standards and models
Developing and implementing genomics-based computational tools that automatically extract clinical genomic evidence from variant interpretation to reduce manual curation
Generating evidence from research focused on end-user prioritized use cases to standardize both dynamic genome annotation and its interpretation for clinical care

Table 4. Long-term projects (4–5 year timeline)

Developing efficient, portable, and user-friendly storage of genomic and genomics-based information for clinical use
Studying genomics-based CDS tools and resources that ensure equitable implementation so resource-limited communities are not left behind
Developing and assessing the value proposition for genomics-based clinical informatics systems
Developing and implementing genomics-based interfaces between laboratory information systems and the electronic health record
Identifying and addressing barriers related to the establishment and implementation of genomic exchange systems

GCIT research requires both scalable and sustainable infrastructures to foster a robust exchange of genomics-based health information. However, there currently is not an agreed-upon approach in establishing such infrastructures. There is a need for developing scalable, sharable, and computable genomic knowledgebases that are harmonized with practice guidelines and clinical workflows. Cloud-based platforms offer a potential solution to address the scalability needs of the GCIT community.[12–14] For example, The NHGRI Genomic Data Science Analysis, Visualization, Informatics-Lab space (AnVIL) is a cloud-based resource developed to analyze, store, and share genomic, as well as associated clinical and molecular data for the basic and clinical genomics research community.[15] However, research is needed to understand better how the clinical community can leverage cloud platforms to address costs and efficiency while balancing accessibility and security.[16]

Shareability is essential for the access and representation of data. Currently, there is no single standard for representing genomics-based information in a structured format that is commonly integrated into the EHR. Several groups, including the Health Level Seven International® Clinical Genomics Work Group,[17] Sync for Genes,[18] and the GA4GH,[19] are working in this area. NHGRI has also encouraged efforts to develop ways to leverage the HL7 FHIR® specification to represent genomics-based information,[20,21] as well as efforts to develop and implement technical standards for the interpretation and reporting of genomic variant information for clinical use.[22] However, additional research is needed to better understand the barriers that hinder the development and implementation of genomics-relevant standards into EHR and CDS systems. Standardized approaches to implementing CDS in the EHR, including valuable tools such as Open Infobutton[23] and CDS Hooks,[7] are 2 examples developed to address these barriers. The role of Infobuttons has been studied in the context of genomics,[23] but implementation in EHR systems remains limited. Research on improving the processes for integrating and evaluating new genomics-based data elements for either limited or extensive use in EHR systems has the potential to be incorporated into the United States Core Data for Interoperability.[24] Therefore, the clinical informatics community should stimulate a multidisciplinary research agenda that creates sustainable and scalable infrastructures to support genomic data collection and its use in a standardized manner. Such an agenda can also address key issues such as interconnectedness, security, establishing a networked ecosystem, and privacy concerns while promoting research, empowering patients, and promoting diversity.

Development and evaluation of outcomes that are important to researchers and stakeholders should be included when producing plans to develop and implement GCIT for the clinical genomics research community. Stimulating research in these areas will assist in developing and standardizing methods for integrating genomic data into clinical settings and address barriers associated with the "last mile" of implementation—actually getting GCIT into clinical use. In addition, such research coupled with novel approaches, like business case analysis, will aid in revising the current business models to encourage the development, implementation, and sustainability of open source genomics-based tools and resources. Healthcare provider decision-makers should also be engaged to determine what evidence is required to increase institutional funding of GCIT. These efforts will assist in identifying the critical research needed in improving the economics of developing and implementing GCIT.

Based on the presentations and discussions covered during the GMXIII meeting, several valuable research opportunities were identified. These projects were parsed into those that might be completed in short-term (1–3 years) and long-term (4–5 years) timelines (see Tables 3 and 4, respectively).

The GMXIII and GMVII meetings provided members from the informatics community to identify opportunities for improving GCIT in clinical care. However, both meetings had limitations. For example, both meetings had an emphasis on engagement in future research and included attendees who were familiar with the subjects covered in both workshops. The workshops' emphasis and invited attendees introduced a bias since they represented mainly early adopters and innovators and not the broader informatic community. Also, both surveys had a good response rate from participants but there is always the issue of different perspectives in the nonresponders which are not captured. To mitigate this concern, the meetings were organized to provide extensive time for broader participation and discussion. This also allowed for participants to identify emergent themes that were not captured in the surveys.

CONCLUSION

The GMXIII meeting, building on initial ideas arising from GMVII and incorporating priorities from the 2020 NHGRI strategic vision, summarized, identified, and prioritized the critical knowledge gaps in the development, implementation, and evaluation of GCIT. While many challenges from GMVII persist, new priorities were identified in the areas of equity and inherent bias, end-user engagement in the context of real-world clinical use cases to develop solutions that are more likely to be implemented, and sustainability of open-source solutions. Incorporating a broader range of methods that draw from disciplines such as implementation science, outcomes research, business case analyses, and other disciplines is needed to emphasize pragmatic approaches to research questions. These are all aligned with the 2020 NHGRI strategic vision and will be important in guiding future research.

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AUTHOR CONTRIBUTIONS

All authors contributed to the conception, design, and implementation of the workshop. KW, MSW, and LF drafted the original draft of the manuscript. All authors reviewed and provided edits to the manuscript. KW and MSW revised the manuscript to incorporate edits and comments from authors. All authors approved the final version of the manuscript.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *Journal of the American Medical Informatics Association* online.

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CONFLICT OF INTEREST STATEMENT

Dr. Relling and St. Jude receive investigator-initiated research funding from Servier. Mr. Aronson's employer, Mass General Brigham, receives royalty payments on sales of GeneInsight software. All other authors have no competing interests to declare. Ms. Bastarache receives royalty payments from Nashville Biosciences and is a consultant for Galatea Bio Inc.

DATA AVAILABILITY

Data presented in this article are available in the article and in its online supplementary material. The agenda, presentations, and information regarding the GMXIII meeting are also available at: https://www.genome.gov/event-calendar/genomic-medicine-xiii-developing-a-clinical-genomic-informatics-research-agenda. Presentations, agenda, and information regarding the GMVII meeting are available at: https://www.genome.gov/27558904/genomic-medicine-centers-meeting-vii

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