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Education and Electronic Medical Records and Genomics Network, Challenges and Lessons Learned from a Large-Scale Clinical Trial Using Polygenic Risk Scores

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REVIEW

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ABSTRACT

Polygenic risk scores (PRS) have potential to improve health care by identifying individuals that have elevated risk for common complex conditions. Use of PRS in clinical practice, however, requires careful assessment of the needs and capabilities of patients, providers, and health care systems. The electronic Medical Records and Genomics (eMERGE) network is conducting a collaborative study which will return PRS to 25,000 pediatric and adult participants. All participants will receive a risk report, potentially classifying them as high risk (~2-10% per condition) for 1 or more of 10 conditions based on PRS. The study population is enriched by participants from racial and ethnic minority populations, underserved populations, and populations who experience poorer medical outcomes.

All 10 eMERGE clinical sites conducted focus groups, interviews, and/or surveys to understand educational needs among key stakeholders—participants, providers, and/or study staff. Together, these studies highlighted the need for tools that address the perceived benefit/value of PRS, types of education/support needed, accessibility, and PRS-related knowledge and understanding. Based on findings from these preliminary studies, the network harmonized training initiatives and formal/informal educational resources.

This paper summarizes eMERGE's collective approach to assessing educational needs and developing educational approaches for primary stakeholders. It discusses challenges encountered and solutions provided.

Introduction

The electronic Medical Records and Genomics (eMERGE) network was established in 2006 and aims to develop, disseminate, and apply approaches to research that combine biorepositories with electronic medical record (EMR) systems for genomic discovery and genomic medicine implementation research. In July 2020, Phase IV of the eMERGE program was launched with the objective of recruiting 25,000 participants across 10 clinical sites—all of whom will receive a risk report that includes polygenic risk scores (PRS), monogenic risk (adults only), family history, and clinical risk factors. The report is called the Genome Informed Risk Assessment (GIRA).

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Unlike a single research study focused on a specific condition or population, the results of the eMERGE study will inform not only how PRS can be used to identify people at high risk for common conditions but, importantly, if receiving this risk information helps patients and their providers make health care decisions to improve the patient's overall health. With minimal stated exclusion criteria (eg, unable to consent, recent bone marrow transplant, or no medical record at recruitment site), participants are not selected for presence/absence of disease or susceptibility to disease. They span a wide spectrum of ages (3-75 years) and are geographically diverse, recruited from health care centers across the United States (though biased toward proximity to recruitment sites in large urban areas in which eMERGE sites are based).

In selecting phenotypes for PRS-based return of results (RoR), network leaders prioritized the need to generate feasible, actionable, and translatable scores for individuals across 4 groups: African, Asian, European, and Hispanic/Latino. PRS for a range of phenotypes are promising for their potential to improve health care/outcomes and have been shown to outperform clinical predictors for several diseases.[1-3] Supplemental Table 1 summarizes the final conditions and thresholds/logic for return. Although conditions such as breast cancer and coronary heart disease are relatively mature in terms of the validity and potential for clinical application of relevant PRS, other conditions are less well established. For this reason, the network collectively conducted an extensive process of PRS validation for all phenotypes. Phenotype selection and validation processes are summarized elsewhere.[4]

Returning PRS for multiple conditions, in a clinical environment, is relatively novel. Best practices are only beginning to take shape, though forerunners such as the Polygenic Risk Score Reporting Standards, a joint collaboration between the Clinical Genome Resource (ClinGen) Complex Disease Working Group,[5] have been influential. As outlined in Box 1, eMERGE's custom GIRA report classifies participants at "high risk" (or not) for 11 conditions, based on a range of risk factors. For 10 of the 11 conditions, PRS are the primary driver of high-risk reporting and for most are prerequisite to returning other risk factors such as family history and/or clinical history for most conditions (ie, for most conditions, high clinical/family history risk is not returned in the absence of high risk PRS—see Supplemental Table 1 for more details). The relative novelty of returning and integrating PRS for multiple conditions represents an exciting research opportunity but also poses educational challenges.

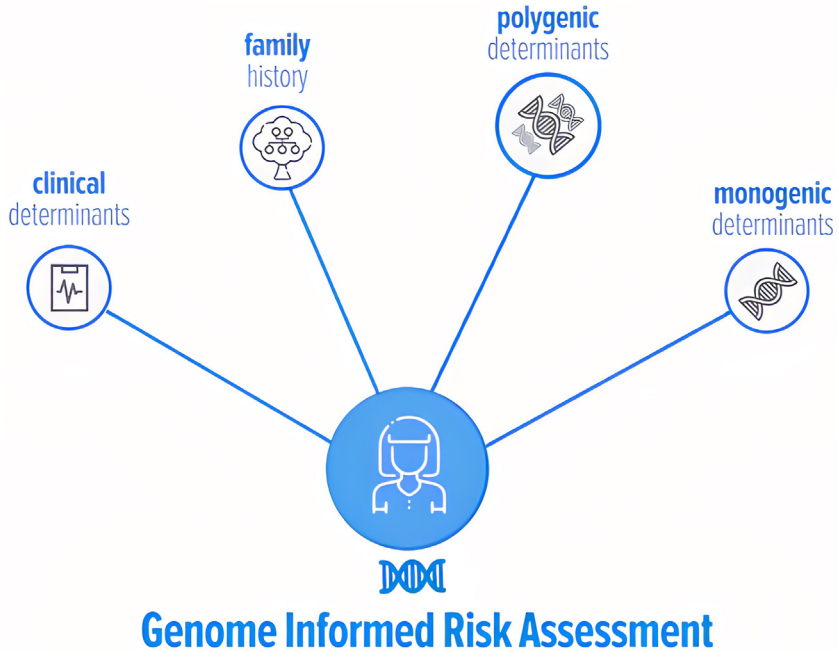
Importantly, PRS performance differs by group. Scores for many conditions were originally developed using genotypes from individuals of European ancestries and therefore tended to perform better in European cohorts.[6-8] A major goal of the eMERGE network is to tackle a long-documented bias in who participates in genomics research. In the US where health disparities are significantly higher than in other high- and middle-income countries,[9,10] it is especially important that PRS-linked phenotypes be validated in historically underrepresented cohorts. Per the relevant National Institutes of Health Requests for Application (HG-19-014), "Minority" (also non-European ancestry) refers to individuals from the following populations: African American or Black, Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, or Latino/Hispanic. Six of the 10 eMERGE sites aim to recruit at least 75% of their participants from racial or ethnic minority populations, underserved populations, or populations that experience poorer medical outcomes. The remaining 4 sites have a 35% recruitment target for minority/underserved communities. PRS for all conditions implemented in eMERGE-IV were validated across at least 2 of 4 groups (African, Asian, European, and Hispanic/Latino). From an educational perspective, network members agreed upon the importance of both acknowledging the historical shortcomings of the genomics community in delivering equitable resources and the urgent effort to address this imbalance. Multiple clinical sites led independent projects engaging local communities and underrepresented populations to assist in designing educational materials and approaches, recruitment strategies, and offer guidance on study implementation. Additionally, the eMERGE network has been transparent about the fact that not all PRS are validated for all 4 groups.

In addition to marginalized racial and ethnic populations, eMERGE has made efforts toward inclusion of people with disability, in which health disparities are among the largest in the United States.[11] Despite research indicating that many people with disability express high interest in participation in precision medicine research, they often also experience numerous barriers for participation in mainstream research.[12] Key barriers include accessibility of facilities and study materials and limited knowledge among researchers and research staff about how to design inclusive studies. To address some of these challenges, eMERGE collects self-reported disability status information among other demographic questions in its baseline survey. The development of educational material for the network similarly considered issues of accessibility.

Overall, PRS will be returned to a large cohort (N = 25,000), therefore requiring scalable educational resources. Across all sites, approximately 24% of research participants are expected to be classified as high risk for at least 1 condition (see Supplemental Table 1), necessitating coordination between clinical sites for consistency in study design and risk reporting.

The latest phase of the eMERGE program constitutes a model of genomic medicine that is potentially generalizable and scalable to a large proportion of the US population and other countries with genomics capacity and access to EMRs. Education will be a key component in helping to develop a comprehensive suite of resources and know-how that support the use of genomic information in clinical care of diverse populations. It will also be critical for promoting team-oriented genomic care, encompassing patients,

Box 1. Main elements of the genome-informed risk assessment (GIRA). Genetic results, along with family and medical history are used to estimate participants' risk of developing 11 common conditions (Supplemental Table 1). The GIRA can classify participants at "high risk" of developing a condition based on several factors. For 2 conditions (break cancer and CHD), an integrated absolute risk score is presented; for the others, the information is displayed separately.[4] Note, in addition to the GIRA, a PRS report and monogenic report (if relevant) are produced separately and appended to the GIRA.



Polygenic results: In eMERGE, PRS are calculated for 10 of the 11 conditions implemented. Each phenotype has a specific PRS percentile cut-off (2%-10%) that is associated with high risk. The participant's exact percentile is not provided. For breast cancer and coronary heart disease, PRS are integrated with other risk factors to achieve a global score, incorporating the other risk elements discussed below. Breast cancer used the BOADICEA model.[20]

Monogenic results: Adult participants (18+ YO) provide an additional biosample, which is assessed for monogenic susceptibility across a 16-gene panel. Relevant conditions tested are the following: Constitutional mismatch repair deficiency syndrome (CMMR-D), Lynch syndrome, *BRCA1/BRCA2*-Associated Hereditary breast and ovarian cancer (HBOC) syndrome, *PALB2*-related conditions, *PTEN*-related conditions, Li Fraumeni syndrome (LFS), Peutz-Jeghers syndrome (PJS), Familial hypercholesterolemia (FH), and LMNA-related conditions.[21]

Family history: Participants are asked to provide their family health history for all conditions using an online tool called MeTree, developed at Duke University.[22] For some conditions (eg, coronary heart disease), positive family history alone can trigger high risk. For other conditions (eg, hypercholesterolemia) positive family history is returned only if a participant is at high PRS/monogenic risk for the same condition.

Clinical risk factors: Data from participant self-report surveys and the EMR will be used to calculate risk, or contextualize high genetic risk. Examples of these clinical risk factors include most recent hemoglobin A1C, reported physical activity, and BMI, when available. Similar to family history, high risk for any given condition is only returned if a participant is at high PRS/monogenic risk for the same condition.

research participant, health care provider, or study team member. The experiences, processes, and lessons learned from eMERGE IV can shed light on these issues and inform other consortia that are considering similar issues or related work.

A crucial component of this coordinated approach is the need to understand and subsequently address the educational requirements of eMERGE participants, providers, and site representatives (eg, study coordinators, recruiters, and clinical staff returning results). For this purpose, an Education Subgroup was created to develop and coordinate the work surrounding educational material. The Education Subgroup comprises members from all eMERGE sites and diverse expertise. This paper will review the network's collective approach to education through needs assessment and subsequent resource development. It specifically

addresses (1) assessment of educational needs around PRS, (2) the process of developing educational resources, and (3) challenges and lessons learned.

Assessment of educational needs around PRS

To facilitate RoR and study coordination, eMERGE leaders developed a range of initiatives to understand and address educational requirements for its many constituents as summarized in Table 1. Key to these were Ethical, Legal, and Social Implication (ELSI) studies conducted at member sites in the first 2 years of the eMERGE study. These ELSI studies differed in scope and methods used (eg, interviews or focus groups) but all explored perspectives and needs related to study implementation. Ultimately, these studies informed the development of educational resources, which are summarized in Table 2. The resources address eMERGE's primary stakeholders: patients/participants, providers, and study teams.

In addition to the wide-range of ELSI studies that informed study design and relevant educational initiatives, a huge effort was undertaken across the network to solicit input from a broad spectrum of individuals. Sites directly engaged with different community groups and advisory boards, including those representing Black/African American community members, pediatric- and adult-specific subcohorts, health care providers with a range of backgrounds, and hospital leadership. Collectively, these generated feedback on study design, knowledge of genetics, and interest in participating in the study. Feedback from these groups, though not (necessarily) captured in "formal" research design, provided important discussion points for consideration by eMERGE education leadership.

Development of educational resources

Design of the GIRA

All 25,000 participants across the eMERGE network will receive a novel report - the GIRA. This includes approximately 6000 participants expected to be identified as high risk. The GIRA was custom-developed for returning results to participants, with relevant features including PRS, monogenic risk, family history, and clinical risk.

In developing the network-wide risk report, several features specific to the eMERGE study were important to consider, including the novelty of the study objectives (particularly PRS), the diversity of participants, (particularly in terms of race, ethnicity, and age), and the different backgrounds/needs of providers and patients in interacting with relevant content. The goals of the GIRA were to inform participants of their study results, to provide educational material about the associated condition, and to provide care recommendations for the participant and their provider. Individual eMERGE sites drafted risk report language and recommendations for the condition(s) led by that site. Relevant material included educational content to help patients/providers understand the conditions, the implications of their risk result, and available options for next steps to reduce high risk. This approach was the most pragmatic because it allowed the network to leverage local expertise and resources specific of the site(s) leading respective conditions. However, it yielded substantial variability in the requisite detail and language level. Once drafts were created, a GIRA development subgroup worked to standardize the language and graphics for all 11 eMERGE conditions.

Educational resources for research participants

Concepts such as "monogenic" and "polygenic" risk are unlikely to be familiar to this broadly healthy research cohort, presenting a challenge for returning results—particularly for individuals not identified as high risk, who may not have the opportunity to discuss results with a health professional. Informal education resources can play a major role in addressing this issue. Surveys show that the majority of internet users in the United States use online sources as their primary source of health information.[23,24] However, the lack of reliable information has been well documented, sowing distrust among users.[25] Authoritative print, video, and internet multimedia developed by universities, hospitals, and science centers can help to address the communication gap between research/medical communities and the general public. A large consensus in the scientific community favors the free dissemination of information as widely as possible.[26] To this end, the eMERGE network clinical sites developed educational materials for online dissemination, aiming to engage participants to be fully informed decision makers throughout their participation.

Study website. Much of the educational content produced for the GIRA, along with many other efforts across the network, was repurposed for a participant-facing website www.emerge.study. This website organizes the broad spectrum of participant-facing educational materials in one location for current and prospective participants to reference. Participants can use this website throughout their participation in eMERGE, from finding contact information for their site to register for eMERGE, all the way up to viewing the GIRA frequently asked questions (FAQs) and condition-specific education pages while waiting for their results.

In creating the web resource, an eMERGE web team discussed scenarios most likely to be relevant to users, agreeing upon 4: (1) prospective participants interested in learning more about the study, (2) enrolled participants interested in learning about next steps or discussing questions, (3) individuals looking to contact a local eMERGE site for any reason, and (4) providers with questions about the eMERGE study and/or GIRA recommendations. A dedicated section was built around each of these scenarios with separate FAQs for providers/participants, and similarly distinct discussion of study protocols tailored to respective users.

All material was created in both English and Spanish and made openly-available to the general public, with no requirements for registration. Before launch, usability-testing

Table 1 Key eMERGE stakeholders and respective educational objectives. A one-size-fits-all approach to education is unsuitable for a program involving heterogeneous stakeholders with disparate educational objectives. Acknowledging the numerous constituents across the research clinical-spectrum, the eMERGE Education Subgroup identified 3 primary target groups: research participants, research staff, and health care providers. These groups have necessarily different competencies and priorities, which require targeted approaches to capturing learning needs and developing educational resources. This table summarizes the main research considerations considered for each group and the respective educational objectives addressed:

A. General public: Broadly healthy population. Non-medically oriented individuals.
B. Health care providers: Medically-trained individuals working in the clinical domain. The individual will have direct contact with the eMERGE participant as a patient at their clinical site. However, 2 important criteria are consistent across the network: (1) High risk reports are returned in-person; (2) Reports that do not include a high-risk result are returned to the participant without in-person consultation.
C. Study staff: Medical- and/or research-orientated individual that is a member of an eMERGE[a] clinical or support center[b].
Unless explicitly stated, the points delineated below arose from eMERGE's preliminary ELSI studies.

A. Research Participants:

Research Considerations	Objective(s) of Educational Resources	Relevant Findings and Lessons Learned
Develop a novel risk report (the GIRA) that integrates PRS, monogenic risk, family history, and clinical risk factors.	Ensure patient-participants understand the risk report (GIRA).	• Patients may struggle to understand PRS-based reports.[13] • Misinterpreting percentiles as absolute risk is a common mistake.[13] • Patients prefer absolute risk information and a continuous result (vs, high risk/not high risk) report design.[13] • Patients have a preference for visualization.[13] • Patients/community members express a need for simple language,[13] including Spanish versions among target sub-cohorts.
All 25,000 participants will receive a GIRA risk report. Of these, ~6000 will be identified as high-risk for 1 or more conditions	Avoid harm by worry. Avoid false reassurance for individuals not at high risk.	• Clarify that "high risk" and "low risk" are not indicative of a diagnosis. • For high-risk participants, results should be returned directly by a genetic counselor, physician, or trained clinical research professional. • Provide system navigation for those who are at high risk For participants not at high-risk for any conditions, results can be returned to the EMR and/or by letter. In this instance, education is reliant upon the clarity and comprehensiveness of the risk report, and supplemented by informal educational resources including brochures, video, and study website.
Facilitate easy access to reliable information about PRS and the eMERGE study	Develop accessible study website to engage participants to be fully informed decision makers throughout their entire participation.	• Delineate subsections likely to be relevant to users. For eMERGE this includes: ○ Prospective participants interested in learning more about the study. ○ Enrolled participants with questions about next steps. ○ Individuals looking to contact a local eMERGE site. ○ Providers with questions about the eMERGE study and/or GIRA. • Translate content if targeting a sub-cohort with different language capacity. • Apply usability testing to address functionality, clarity, and relevance. • Capture and review analytics.
Minority Enriched: Six of the 10 eMERGE sites aim to recruit at least 75% of their participants from racial or ethnic minority populations, underserved populations, or populations who experience poorer medical outcomes.	Provide cohort-appropriate educational material and approaches.	• Leverage off-line forms of communication, including community-based newspapers, magazines, and radio. • Opportunities for interpersonal conversations are important for participants of racial or ethnic minority populations for responding to questions and concerns. • Per above, Spanish versions of educational material can help target sub-cohorts.

(continued)

Table 1 Continued

A. Research Participants:

Research Considerations	Objective(s) of Educational Resources	Relevant Findings and Lessons Learned
Age Spectrum: Participants span a pediatric-adult age spectrum (3-75 years). Pediatric and adult participants receive different GIRA reports, with different conditions relevant to each. In addition, adults will receive a monogenic risk report for a discrete number of conditions.	Understand needs of different sub-cohorts in terms of expectations. Communicate clearly implications of respective phenotypes.	• Parents face barriers in acting on recommendations,[14] which reflect previously-reported limitations for minority and underrepresented communities.[15,16] Perhaps the most notable barrier that participants reported was existing behavioral health issues in their children. Given the high prevalence of conditions such as ADHD (9.4%),[17] behavioral conduct (7.4%), and anxiety problems (7.1%),[18] behavioral health clearly needs to be taken into consideration when strategizing risk reduction in children. • Younger participants (20s and 30s) may be lower resourced and/or less motivated to address a risk in the future (vs older participants).

B. Healthcare Providers

Research Considerations	Educational Objective(s)	Relevant Findings and Lessons Learned
Large-scale return of results leveraging PRS is novel.	Improve genomic knowledge by providing templates and resources to facilitate return of results and recommendations for follow-up care. Provide educational resources that can be shared with patients.	• Providers probed for their reactions to PRS reports of different designs, reported that[13]: ○ The report is more than just communicating a result, but integral to the whole interaction with the patient. ○ The Limitations section of the GIRA report should make it very clear what these mean for the patient. ○ Education can help in becoming comfortable with their "spiel." • Providers request different types of educational materials—some that would enhance their own knowledge and some that could be shared with patients.
Primary care providers and health care providers may not be aware of the eMERGE study	Provide as-needed resources to support encounters in which the program may be unfamiliar. Provide an online resource that clearly outlines program goals and report implications.	• Many PCPs are inexperienced with PRS and may feel uncomfortable using it in clinical practice. In particular, clinicians may not be comfortable returning results that are not within their immediate expertise and they have limited time to do so. • PCPs express a preference for easy to use, non-time-consuming material—preferably, info that can be found by clicking a link and consumed quickly (eg, versus watching a video). • Many providers would prefer forewarning of pending genetic report information • Endorsement or actual guidelines from relevant specialty societies would promote trust in test reports. • Some providers were interested in technical information regarding GIRA development, available outcome data, and other published research. Links to peer reviewed journal articles would promote trust in the test reports. • Online resource should include the following: ○ Sources for guidelines and recommendations. ○ Contact details for local teams. • Supporting educational initiatives preferred by providers include: ○ An online webinar with CME. ○ Available online recording. ○ Separate online webinar to practices where recruitment will be high. ○ The option to provide in-person "lunch and learn" sessions. ○ Modeling of results return by a PCP for both high- and low-risk scores.

(continued)

Table 1 Continued

B. Healthcare Providers		
Research Considerations	Educational Objective(s)	Relevant Findings and Lessons Learned
Provide clinical decision support: (CDS) to facilitate reporting and downstream health care implementation	A well-designed CDS development and validation plan can facilitate implementation of PRS-based recommendations.	• Reflecting a theme from previous work,[19] PCPs expressed a desire for CDS targeted to primary care that may include actionable steps in the EMR such as the following: ○ Modification of the problem list. ○ Reviewing provider education. ○ Provision of patient-family education. ○ Referrals to specialists, and/or ○ Ordering a preventive medication.
C. Study Staff		
Research Considerations	Educational Objective(s)	Relevant Findings and Lessons Learned
Recruiters, Coordinators, Resource Developers, and Other Research Staff are highly diverse in terms of background, experience, and training. Staff require answers regarding study components and key research objectives. Need for accessible educational resources that address misperceptions.	Disseminate standard resources/ messaging across the network.	Collective need to coordinate and share know-how and resources. Core elements required for centralized access: • (Electronic) data capture and tracking. • (Electronic) consent driven by a single IRB. • Standard operating procedures (SOPs) for sample management and ordering, and engagement. • Provision of regular training. A centralized database accessible to clinical sites can streamline and standardize Network supports (eMERGE utilized REDCap for this purpose): • Support data integration from third-party providers for shared SOP development and to facilitate collective testing and training.

[a]Clinical sites: Children's Hospital of Philadelphia (CHOP), Cincinnati Children's Hospital Medical Center (CCHMC), Columbia University, Mass General Brigham, Mayo Clinic, Mount Sinai, Northwestern University, University of Alabama At Birmingham, University of Washington, and Vanderbilt University Medical Center.

[b]Support Sites: Coordinating Center: Vanderbilt University Medical Center; Genotyping Center: Broad; Monogenic Sequencing: Invitae; Family History: MeTree (Duke University).

was performed on a small convenience sample of individuals ($N = 5$), which addressed functionality, clarity, and appropriateness of resources, yielding minor revisions in content structure and language. To monitor usage of the site, analytics are captured and reviewed on a monthly basis, with the opportunity to formatively adapt to relevance/popularity of content on an ongoing basis. (However, it is a requirement of the central institutional review board [IRB] that all study material on the website be approved by the IRB, necessarily limiting the speed with which any content can be updated.) The site follows Section 504 of the 1973 Rehabilitation Act to prevent discrimination on the basis of disability. Care was taken to ensure broad representation in images, including diversity in race, ethnicity, disability, gender, and age. This approach was similarly applied in developing other content for dissemination across eMERGE stakeholders (brochures, flyers, etc.).

Education resources for health care providers

In addition to receiving the GIRA directly (either through a patient portal or by mail), high-risk participants are contacted by a genetic counselor, clinician, or trained health professional, who recommend that the high-risk participant follows up with their local primary care provider (PCP) where additional testing/referral may be required. Importantly, the majority of PCPs across eMERGE will likely be naive to the eMERGE study and may encounter the GIRA for the first time during a clinical encounter with a participant-patient. A range of educational approaches are therefore required to support providers in discussing and acting upon GIRA health care recommendations.

We learned from our ELSI studies that, though comfortable explaining risk to patients, many PCPs are inexperienced with PRS technology and may feel uncomfortable using it as a tool in clinical practice. They also expressed concerns about being caught "off guard," not having heard about the study in advance, and they had questions and concerns about the validity of the PRS and implications for prevention and treatment. This gap between knowledge and practice with PRS is a potential obstacle for uptake among providers, with downstream ramifications for (possible difficulty in) implementing care recommendations. Moreover, clinicians may not be comfortable discussing results that are beyond their immediate expertise, in particular when time constrained. Rather, they expressed a preference for easy to use, non-time-consuming material, Physicians were also interested in accessible fact sheets for sharing with patients. eMERGE education initiatives that address these findings include the provision of clinical decision support (CDS), development of custom web content,

Table 2 Resources developed by eMERGE network sites. Unless otherwise stated in Column 1, relevant resources are used network-wide by all eMERGE sites (resources delineated as site-specific were nevertheless shared with network partners).

Resource	Stakeholder	Description
GIRA Report	Participant and Provider	The GIRA (Genome Informed Risk Assessment), the novel result report issued in this study, caters to both patients and providers through its accessible phrasing and diagrams, as well as separate FAQ sections for participants and providers.
Infographics	Participant	Infographics were developed through an iterative process, including 10 "think aloud" sessions in English and Spanish with community members. The infographics explain the components of a GIRA, the meaning of genetic predisposition for a disease, and general recommendations for both high-risk and not at high-risk individuals.
Participant and Provider facing website (www.emerge.study)	Participant and Provider	The website is a resource for participants to learn about the goals of the study, the timeline of participation, and information about results. A subgroup led by CHOP was formed to spearhead the development of the website. They used the services of third-party vendor Culture Shift to design the website and translate it into Spanish. In addition, the website follows requirements for disability accessibility
Participant and provider FAQ's/patient education pages	Participant and Provider	Centrally-developed educational material included a plain-language brochure, common FAQs, and patient/provider education pages for use across the network.
Clinician education resources (site-specific)	Provider	Several sites developed local CDS to facilitate on-demand education, focused on implementing GIRA guidelines. Although network members shared expertise and methodologies, individual sites developed individualized CDS to align with local institutional infrastructure and policy.
Bilingual content	Participant	Although not a "resource" in the traditional sense, the provision of educational material in Spanish as well as English was important to addressing representation and included here as a core component of Education strategy.
Animated recruitment video to explain eMERGE	Prospective participant	Animated 2-minute video developed by collaborators across the Network and made available to all prospective and existing participants.
Participant-facing online presentations/webinars [site-specific]	Participant	Two sites made short (~7-minute) presentations available to (prospective) participants. These focused on explaining PRS, their clinical use, and current limitations, including increased accuracy in populations with origins from Europe compared with other populations. They also defined genetic terms, such as 'DNA', 'gene', and 'genetic variants'. Additionally, a vignette where a patient was offered a PRS for hypercholesterolemia was incorporated to help contextualize the application of PRS for common health conditions
Provider-facing in-person presentations [site-specific]	Provider	Provider-facing presentations introducing eMERGE study, implementation, and basic concepts around PRS were given at primary care recruitment sites (a) at the start of recruitment and (b) leading up to return of results. Presentations also directed providers to the eMERGE.study website and staff contact information. Presentations were given at grand rounds, lab-meetings, departmental meetings, and scheduled informational sessions.
Provider-facing online presentations/webinars [site-specific]	Provider	Following the same format as in-person presentations, 15 to 20-minute webinars were recorded and made available online for provider access.
Provider-facing PRS online media	Provider	Easily navigable online resource containing practical information about the study, specifically designed for use during routine patient care activity.
Clinical hotline [site-specific]	Provider	One site developed an expert clinician hotline to connect clinicians with study experts to address any questions related to study results.
Staff-facing PowerPoint	Study Team	PowerPoint presentation given to all eMERGE research staff members. Disseminated Network-wide over a series of "classes" to introduce the basics of eMERGE and create a shared baseline of knowledge amongst staff members. Creating these slides was a network wide effort undertaken by the education workgroup. The presentation was given by multiple members of this workgroup.

(continued)

Table 2 Continued

Resource	Stakeholder	Description
Research assistant office hours	Study Team	Biweekly meetings open to any Network member focused on answering the questions and addressing the concerns of coordinators/recruiters/research assistants. Open space to solicit advice from others and collaboratively solve problems and share tips.
Centralized staff support and training	Study Team	The Network Coordinating Center hosted frequent education/training program for staff at all sites and developed several standard operating procedure documents consisting relevant to study implementation and general utilization of the interface.
Return of return of result staff training materials	Study Team	Several tools were created by the Network for return of result staff members to utilize and prepare for the sessions. A content guide was developed to provide staff with educational resources needed to efficiently explain results to participants. Talking points for the various return of result sessions were created to help outline the sessions and to guide sessions. Finally, mock roleplay sessions were held among various members across the Network to allow individuals to practice returning results scenarios in a training environment.
Return of results round tables	Study Team	Biweekly meetings open to any Network member who is involved in the return of results process to discuss shared experiences. Opportunity to gain feedback on how the sessions went and ways to improve the discussion of results.

CDS, clinical decision support; *CHOP*, Children's Hospital of Philadelphia; *eMERGE*, electronic Medical Records and Genomics; *FAQs*, frequently asked questions; *GIRA*, Genome Informed Risk Assessment; *PRS*, plygenic risk scores.

and creation of a range of learning sessions, and are discussed immediately below.

CDS. Interviews with providers at several eMERGE sites indicated a preference for CDS to help implement GIRA recommendations. CDS is an important component of education strategy, addressing the need for continuous and current knowledge in daily practice[27] and can also address the complex sociotechnical factors that arise from genomic test results.[19] Reflecting a theme from previous work,[19,28] interviews with providers underline a desire for CDS targeted at primary care that may include actionable steps in the EMR, such as modification of the problem list, reviewing provider education, provision of patient-family education, referrals to specialists, and/or ordering a preventive medication. PCPs welcomed CDS for positive results only, with a strong preference for clear recommendations and next steps.

Custom web content for providers. To facilitate easy access to reliable information about PRS and the eMERGE study, the emerge.study website was updated with provider-specific content. Interviews with physicians and clinical leaders indicated that links to peer-reviewed papers and endorsement or actual guidelines from relevant specialty societies would make them more likely to trust and use these tests. The site was updated with links to source material and guidelines, on which GIRA recommendations are based. In addition, provider-specific FAQs were published, in which a range of themes included a program overview, the role of the health care provider in eMERGE, the patient/participant experience, and data privacy.

Webinars and other learning sessions. Although recognizing a preference for informal, just-in-time, resources, several initiatives were developed for providers preferring more increased engagement. These are particularly pertinent to health care practices/clinics enriched for eMERGE patient-participants and include the following:

- An online webinar with Continuing Medical Education—several sites offered Continuing Medical Education credits centered on PRS and the GIRA
- Targeted online webinars in practices in which recruitment will be highest
- Provision of webinar recordings available to PCPs online
- In-person "lunch and learn" sessions at practices with a high level of eMERGE participation.

These initiatives were considered necessary to supplement resources that are intentionally not time consuming and providing a more in-depth perspective on the goals and implications of the eMERGE program. Webinars and presentations focused on explaining PRS, their clinical use, and current limitations, including increased accuracy in populations with origins from Europe compared with other populations. Sites focused on recruiting Hispanic individuals offered relevant educational resources in both Spanish and English.

RoR training sessions were developed to help coordinate RoR and to ensure that individuals felt confident to discuss this new form of results. A content guide was developed that collected network resources, including, lecture series, articles, and tools to aid return. Talking points for high-risk pediatric PRS results, high-risk adult PRS results, monogenic results, and edge cases were also generated. The network also provided staff the option to participate in mock roleplay sessions. Potential scenarios and mock GIRAs were generated, and those who wanted the additional practice had the opportunity to gain feedback on ways to better manage the RoR session. Understanding the need for ongoing communication and

feedback about RoR sessions, the network also hosted biweekly round tables for staff members to share experiences and learn from the experiences of others.

Education resources for recruiters and study coordinators

Any large program will require delegation of workload across several subgroups. Although essential from an organizational perspective, an unwelcome consequence is the potential for respective workgroups to become siloed and detached from the broader mission. In the context of eMERGE, this is of particular concern to team members directly interacting with participants and who are required to cogently address participants' questions and concerns. To provide the requisite resources for participant engagement, the network developed and conducted a series of training sessions for coordinator and recruitment teams, which reviewed program goals and approaches and anticipated questions from (prospective) participants. The goal was to ensure study members meet a standard minimum in terms of baseline knowledge of the eMERGE program and implementation requirements.

The primary staff education initiative was developed and coordinated to begin 1 to 2 months before the first participants were enrolled. A 2.5-hour training curriculum was developed for recruiters and study coordinators across all 10 clinical sites and focused on program goals and relevant study themes such as genetics; PRS; disease risk; and limitations of disease risk prediction for certain groups study privacy, study partners, and consent language.

Importantly, a series of formative assessments were integrated into the session, facilitating real-time feedback from attendees, with the opportunity to pivot accordingly. A set of multiple-choice questions addressing the major topics covered in the training sessions were prepared in advance and integrated into a polling feature, which allows the audience members to answer questions and have their answers recorded and displayed for the group. These questions were asked after each topic was presented and used to assess whether the audience had understood the content, reinforce major points, and add additional explanations if indicated.

Coordination. Additional support focused on know-how related to the use of genomic information in clinical care. This leveraged a centralized data capture portal built in REDCap,[29,30] which allowed participants to electronically consent and enter survey data, while also providing sites the ability to track participants and send/receive data from Network data partners. The Network Coordinating Center (Vanderbilt University Medical Center [VUMC]) hosted frequent education/training programs for staff at all sites and developed several standard operating procedure documents consisting relevant to study implementation and general utilization of the interface.

Challenges and Lessons Learned

Although each clinical site necessarily has distinct demographic and institutional priorities, common themes from eMERGE's collective research and approaches have been critical in driving network-wide collaboration. We hope that our shared initiatives can be instructive to other consortia and/or individual sites similarly involved in operationalizing/expanding precision medicine programs and propose several discussion points.

Need for harmonization

Among the biggest challenges, educationally, for eMERGE has been to harmonize the efforts of 10 different sites, operating from 10 different funded proposals, albeit with shared goals. Clinical sites in eMERGE are individually focused on disparate target populations (eg, African, Asian, European, and Hispanic), age groups (adult/pediatric), and institutional priorities. These align with different language or communication preferences. An important part of education strategy is making sure these priorities are all represented and messaging is consistent across groups. Virtually all eMERGE sites used community engagement and input from relevant community groups was important in highlighting requirements, as well as potential gaps in understanding. The importance of consultation with these groups early in the planning process should be stressed because relevant feedback was adopted into educational materials through FAQs, videos, and presentations.

Centralized coordination was critical to the harmonization process. Although somewhat unwieldy from a logistical perspective, the network's use of a single IRB greatly facilitated harmonization of educational material—ensuring all sites were working from a common resource set. Similarly, using a single site (VUMC) to generate the GIRA ensured sites were working from a level playing field in terms of the validity of the final product being returned. This further ensured that content created for patients and providers was applicable to all sites. Similarly, training and educational material for study teams was the same for all sites and based on a report (GIRA) that is consistent for all research participants.

Targeting different stakeholders

A one-size-fits-all approach to education is unsuitable for a program with heterogeneous stakeholders who have disparate educational objectives. Acknowledging the numerous constituents across the research-clinical spectrum, the eMERGE Education Subgroup identified 3 primary target groups: research participants, research staff, and health care providers. These groups have necessarily different competencies and priorities, which require targeted approaches to capturing learning needs and developing educational resources.

Awareness of barriers for participants

A common theme in genetic literature is the difficulty patients/participants have in interpreting risk, and this theme is

borne out again in relation to PRS.[31,32] From an educational perspective, it is clear that resources should be spent determining the extent to which participants understand risk as reported to them, to plainly stress that they are at higher than normal risk where this is relevant, and to simultaneously avoid genetic determinism. Including next steps and ways to reduce risk are practical educational steps that may facilitate implementation.

Relatedly, several ELSI studies in eMERGE identified obstacles participants face in following through on health care recommendations. Collectively, these obstacles stress that the risk result does not exist in a vacuum and that numerous factors can affect a participant's likelihood of following recommendations. For example, for parents of pediatric participants, a high-risk report may need to "compete" with existing behavioral health issues in children.[14] Similarly, adults face competing priorities and as issues of access that influence the feasibility of some recommendations. It is critical that health care providers be aware of such barriers (eg, other medical/behavioral problems or resource/time scarcity) and address them where relevant. Providers interacting with risk reports should be reminded of these factors, whereas recommendations for patients/participants need to be cognizant of the wider psychosocial context.

Finally, these findings underscore the importance of trust between patients and providers. Participants in this study emphasized the importance of access to a trusted resource with whom they could review the results and ask questions.[33]

Cognizance of implementation barriers for providers

Studies from several sites found that clinicians may not be comfortable returning results that are not within their immediate expertise and have limited time to do so. Given the novelty of PRS in the clinical environment, this presents an educational challenge to provider support for RoR, and also prompts ELSI-related discussions on the readiness of providers to interact with these types of results. As mentioned above, the language and formatting of the GIRA is critical to the patient-provider interaction and may be the centerpiece of the clinical encounter. This stresses the need for plain and uncomplicated language, as well as an awareness of difficulties in risk-perception among many participants. Similarly, from a practical educational perspective, the limitations section of the risk report should be very clear on implications for the patient.

The provision of effective CDS can facilitate provider interactions with the GIRA and was highlighted as a requirement among providers in interviews at 2 sites.

Visualization and risk preferences matter

Health and genomic literacy can affect genomic utilization and participation in genomic research, but studies indicate that genomic literacy in the United States is limited.[34,35] Challenges are pronounced for individuals with limited oral, print, or graph-reading literacy and further augmented for individuals whose first language is other than English. Infographics can be an important tool in increasing health literacy[36-38] and in particular addressing deficits in understanding complex health concepts,[37] including genomics and genetic risk factors.[39] For eMERGE, infographics were developed through an iterative process, including modified "think aloud" sessions with English and Spanish-speakers (overall $n = 10$) to explain the components of a GIRA and the meaning of genetic predisposition for a disease, as well as recommendations for both high-risk and not at high-risk individuals.

Centralized training for study teams

Finally, given the novelty, large scale, and wide scope of the project, centralized training of study teams is strongly recommended as an educational output. Clinical and research teams at different sites differ greatly in terms of knowledge, experience, and understanding of study goals and health care best practices. A major effort was undertaken by the coordinating center to standardize enrollment tools and reporting resources, requiring the generation and implementation of SOPs for all major aspects of the program (including, but not limited to, education). Although this effort involves a massive investment of time and human resources, it ultimately yields a standardized protocol, which should greatly facilitate outcomes analyses later in the project.

Assessment

A key component of the eMERGE study is to assess the impact of return of PRS and GIRA results on health care behaviors and outcomes for participants and their providers. It will be essential to re-evaluate relevant educational methods and the clinical utility of the information once outcomes data are available. Toward the end of the eMERGE study timeline, a wide range of studies are planned that address the efficacy and acceptability of the tools and approaches used. Analyses of EHR and self-report data will assess differences in clinical care for participants who received high-risk reports versus those who did not. In tandem, a series of studies across the network will assess outcomes that speak more directly to the efficacy of educational approaches delineated herein. These include interviews with participants (or their parents in the case of pediatric participants), interviews with providers and a network-wide provider survey. Leveraging these approaches, we will assess the extent to which participants and providers struggled to understand reports and act upon relevant information. Although several of the ELSI studies outlined above utilized hypothetical risk report aimed to replicate the RoR scenario, the real-world "road test" will be most critical to relevant outcomes. This will yield formative data and the opportunity to further update educational material/methods for the utility of future PRS-based programs.

A limitation of the eMERGE program pertains to the representativeness of the pilot study participants to the full cohort of 25,000 participants. It may be that findings from the preliminary ELSI studies are biased given that they reflected the views of participants in these small-scale studies rather than the general population. However, similar to the eMERGE network more generally, these preliminary studies comprised primarily of individuals from minority/underrepresented racial and ethnic communities, reflecting a recruitment goal across the 10 clinical eMERGE sites.

Conclusions

In developing a comprehensive education strategy, consideration should be given to (1) the necessity of thinking through the educational needs of different stakeholders, (2) the necessity for different approaches to ascertaining those needs, including targeted studies and stakeholder engagement, (3) that this all takes a huge amount of resources, and (4) that much of what is learnt and developed can be shared across projects, lowering a potentially massive barrier for other projects. For its part, eMERGE is committed to sharing the resources it has put together, which continues to be consolidated as the study progresses, which can be accessed via the network's coordinating center.[40]

Data Availability

Data used in this manuscript are available upon request by contacting the corresponding author. Requests should be sent to the corresponding author with a description of the reason for the request and the qualifications of those requesting the data.

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Ethics Declaration

The studies discussed in this reviewed were all conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board of VUMC and/or local Institutional Review Boards. Informed consent is required from all enrolled individuals.

Conflict of Interest

Emma Perez is a paid consultant for Allelica Inc. Lori Orlando and Tejinder Rakhra-Burris are founders of a company developing MeTree. Maureen Smith is a Section Editor for the Journal of Genetic Counseling. Maya Sabatello serves as IRB member of the All of Us Research Program. All other authors declare no conflicts of interest.

Additional Information

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