National Advisory Council for Human Genome Research (NACHGR)
September 9, 2024
Concept Clearance for NOFOs

Outcomes of eMERGE Genomic Risk Assessment and Reporting

Purpose

NHGRI proposes two RFAs to extend follow-up and collection of outcome data for the 25,000 participants receiving genomically informed risk assessment (GIRA) and management recommendations in the Electronic Medical Records and Genomics (eMERGE) Network. This multi-site continuation of the eMERGE Genomic Risk Assessment and Management Study will: 1) extend follow-up of eMERGE participants from a minimum 1 year to at least 4 years; 2) assess longer-term adherence to and outcomes of GIRA-based preventative recommendations among clinicians and participants; and 3) identify correlates of adherence by condition, participant age and demographics, and social determinants of health.

Background

The eMERGE Network, now in its fourth phase as the eMERGE Genomic Risk Assessment and Management Network (RFAs HG-19-013, -014, -015; Jul 2020-Apr 2026), encompasses 10 clinical sites and a coordinating center. The Network's current goals are multifaceted: calculating polygenic risk scores (PRS) for complex diseases validated in at least two ancestry groups and sharing the results; developing electronic medical record (EMR)-based methods for communicating genomic risk profiles and recommendations for clinical management; recruiting and genotyping 25,000 individuals from diverse ancestries to provide prospective risk assessments for selected conditions; and employing EMR-based evaluations to measure the adoption of risk-reduction strategies and their impact on clinical outcomes.

eMERGE developed GIRA by combining genomic data, family health history, and clinical risk factors in novel ways to estimate a participant's (ppt) risk of 10 common diseases. This required meticulous validation of genomic risk predictions developed primarily in European-ancestry populations for use in the diverse U.S. population. The 10 clinical sites engaged with diverse communities and the clinicians caring for them to tailor risk reporting and management. Investigators combined data from 10 disparate EMRs with genomic data generated by two laboratories, generated standardized reports with care recommendations, and returned them electronically to the 10 sites' EMRs for participants' (ppts) and their clinicians' review.

To date, eMERGE has completed recruitment of 25,375 active ppts, including 4,905 children, with 48% from underrepresented racial or ethnic groups. GIRAs have been returned to 16,609 ppts or their EMRs with return expected to be complete by Jan 2025. As of Jun 2024, observed proportions of ppts at high risk for each condition have met or exceeded expected proportions (2-5% for all conditions except prostate cancer at 10%) for all but hypercholesterolemia and asthma.

Key study hypotheses to be tested across all conditions combined are: 1) proportion of providers recommending risk-reducing interventions will be higher in high risk than non-high risk ppts; and 2) proportion of ppts undertaking interventions will be higher in high risk than non-high risk ppts. With 20,000 eMERGE adults, power is 90% to detect a 3.0-4.7% higher uptake in high-risk ppts (α=0.01), assuming 10-50% baseline uptake in non-high-risk participants. Assuming an overall 25% prevalence of specific high-risk conditions, 15,000 non-prevalent adults would have 90% power to detect an actual 3.4-5.4% higher uptake. Initial data from multiple sites indicate a statistically significant uptake for several conditions including breast cancer, prostate cancer, and diabetes.

Continued follow-up of eMERGE GIRA ppts is scientifically valuable because many of the screening recommendations for the 10 conditions assessed by the eMERGE Network involve repeated surveillance in at least some subgroups every 12 months. Other conditions involve longer follow-up intervals in some or all ppts, such as up to 3 years for chronic kidney disease, up to 2 years for prostate cancer, 4-6 years for hypercholesterolemia, and 2-5 years for Type 1 diabetes. Uptake and sustainability of interventions may differ in those receiving high-risk GIRA results compared to those at lower risk levels or among those differing in demographics (including age), access to healthcare, or social determinants of health.

Due to the complexities of this phase, including validating GIRA for ancestrally diverse individuals, building a data management system able to interface with 10 disparate EMR systems, modifying clinical recommendations to fit the needs of all sites, and recruiting a large and diverse cohort during the COVID-19 pandemic, the original eMERGE timeline has shifted. Even with a one-year extension of the original five-year study, the last ppts to receive their GIRAs will only be followed for 12 months after GIRA return. It is possible, however, that ppt and provider actions as well as effects on clinical outcomes from GIRA return could continue well beyond 12 months. Failure to extend follow-up would underestimate, if not completely fail to detect (for some conditions or subgroups), any impact of GIRA return on clinical management—the primary aim of the study. For these reasons, extended follow-up of the eMERGE GIRA cohort was strongly recommended by NACHGR in Feb 2024 during its review of progress and future directions for eMERGE. A limited competition continuation is thus proposed to follow the cohort and assess longer-term outcomes. During this period, investigators will work to ensure awareness of the need for continued management and monitoring of high risk ppts. At the same time, follow-up data from those not found to be high risk will provide insights on effect of such reports on ppt and clinician behavior.

The resulting data will be used to improve methods and workflows for assessing genomically informed risk and providing this information in user-friendly ways that minimize burden on busy clinicians and maximize ppt understanding and uptake of recommendations. Outcome data will help identify characteristics of ppts, clinicians, and systems associated with improved uptake and potential benefits and harms of receiving this information. These data may also be used to refine genomic risk

assessments and to inform the design of future clinical trials assessing the clinical utility of GIRA-informed approaches to preventive healthcare.

Proposed Scope and Objectives
Two funding opportunities for continued follow-up of eMERGE GIRA ppts are being proposed: a Single Source NOFO for a coordinating center to coordinate and manage data collection, quality control, and analysis; and a second Limited Competition NOFO for 10 clinical sites to continue outcome data collection and analysis. During the continuation, activities to maintain contact and follow-up with current ppts and their clinicians will continue but no new ppt recruitment is anticipated. The Network will also determine the need for updating ppts' GIRA with revised variant classifications as genomic knowledge accrues, updated family history as new familial cases accumulate, and new clinical characteristics as clinical risk factors develop; this may require some additional return of results. Not expected to be part of this effort are activities such as development of new electronic phenotypes, development of new GIRA for additional population groups or unrelated conditions or return of results. However, should investigators identify a compelling need to pursue research in these areas to enrich the quality of outcome analysis, they are encouraged to provide a clear justification for consideration. For those with a keen interest in these domains outside the scope of the proposed NOFOs, alternative support mechanisms are available and may be pursued.

Relationship to Ongoing Activities:
eMERGE will continue implementing and following up genomic risk assessment and management. Unlike the All of Us Research Program, which focuses on resource building without clinical intervention, and the Implementing Genomics in Practice (IGNITE) Network, which conducts discrete genomic medicine trials, eMERGE implements and assesses genomic risk management and uptake by providers and ppts. eMERGE also differs from the Polygenic Risk Methods Development in Diverse Populations (PRIMED) Consortium, which develops new polygenic risk scores and methods. eMERGE outcome data will continue to contribute to PRIMED efforts to refine genomic risk assessments.

Mechanism of Support: Both eMERGE NOFOs will be U01 mechanisms.

Single Source and Limited Competition:
Only the existing awardee(s) funded under RFA HG-19-013, RFA-HG-19-014, and RFA-HG-19-015 will be eligible to apply for the proposed eMERGE continuation NOFOs. The existing awardees will apply independently but will be expected to continue collaborating around the activities required to capture, analyze, report and share outcome data. A limited competition will allow NHGRI to leverage the existing investments made in establishing this cohort and building the infrastructure required to capture and analyze outcomes data.

Funds Anticipated: NHGRI will commit up to $6.0M in total costs per year for four years (FY26-FY29) for a total combined four-year cost of $24M.