National Advisory Council for Human Genome Research

February 12, 2024

Concept Clearance for RFA

Population Screening in Primary Care

Purpose:
NHGRI proposes three RFAs for an implementation and evidence generation pilot program of population screening for common, actionable genomic conditions predominantly in the primary care setting. Specifically, the multi-site program will: 1) select, implement, and evaluate screening for 4-8 genomic conditions in diverse populations and primary care settings; 2) use established strategies for meaningful community engagement in all phases of design, conduct, and evaluation; and 3) develop effective strategies for connecting patients found to have genomic risk variants to follow-up care.

Background:
Screening for genomic variants that substantially increase risk of developing common, complex diseases has been established as a cost-effective strategy for three "Tier 1" genomic conditions identified by the Centers for Disease Control and Prevention (CDC): hereditary breast and ovarian cancer (HBOC), Lynch syndrome, and familial hypercholesterolemia (FH). These conditions at present are poorly ascertained by the healthcare system and patients are often unaware of them until they present with late-stage disease. Several other conditions appear "near-ready" for implementation with accumulating but not yet conclusive evidence.

Primary care providers (PCPs) are in fact, typically the "first line" for managing preventive care—counseling patients on the need for screening, ordering the tests, and linking patients to appropriate follow-up care. While there may be some positive attitudes, the primary care workforce in general feels poorly prepared to address genomic testing and screening [PMID: 23390885], but approaches are available to improve their readiness [PMID:28654958]. Gaps for this workforce include efficient workflows, knowledge, confidence, and a robust informatics infrastructure to support decision-making. These gaps can be bridged by linking clinical centers experienced in providing genomic screening with PCPs to provide needed education, workflows, referral pathways, just-in-time clinical decision support (CDS) and other informatics support tools. Introducing genomic testing gradually into the primary care space, picking a few high-value, high-evidence screening tests that are straightforward to implement and understand, is likely to be more successful than adopting a very large number (such as the current ACMG 3.2 secondary findings list) all at once. Cost-effectiveness of screening has been shown to increase when multiple conditions are assessed simultaneously [PMID: 37155986], taking advantage of a single genomic screen and results return process. Importantly, effective screening also requires establishing effective referral systems for follow-up care.

Community engagement, defined as the process of working collaboratively with a community to address issues that impact the well-being of the group, is critical to conducting successful genomic research and providing effective care, particularly in marginalized communities [PMID:30054469]. This entails proactively seeking out community values, concerns, and aspirations, then incorporating those into decision-making and establishing meaningful, ongoing partnerships. Implementation science can be used to

evaluate engagement across a number of different stakeholder types, including patients, families, communities, clinicians, health systems, and payers.

In November 2023, the Genomic Medicine Working Group of the National Advisory Council on Human Genome Research convened leaders in genomic medicine and related fields in its 15th Genomic Medicine (GMXV) meeting to examine the current state of population genomic screening in the U.S. The group explored obstacles, opportunities, and new directions to inform expanded screening. A strong recommendation of the GMXV meeting was to support pilot studies of implementing population screening for Tier 1 conditions in primary care as well as near-ready genomic conditions that need that "last mile" of evidence to justify implementation. There was consensus that polygenic risk was not yet ready for population screening and this effort should focus on screening for monogenic conditions. They recommended the genomics community engage with the prevention research community to co-develop these genomic prevention research projects.

Proposed Scope and Objectives:
The program will consist of a Coordinating Center (CC), a Sequencing Center (SeqC) and 4-6 Clinical Groups (CGs) experienced in providing genomic testing and interpretation, teamed with PCPs working in diverse settings (e.g. community hospitals, family medicine clinics, and primary care practices) and populations (e.g. patients from racial or ethnic minority, underserved or with poor medical outcomes populations). Awardees will collaborate to select, implement, and evaluate screening of unselected adults for roughly 4-8 genomic conditions with the strongest evidence for effectiveness of screening in preventing disease or reducing its severity. Using principles of implementation science, they will examine methods for conducting this screening in primary care and evaluate them using an implementation framework to be chosen by the program Steering Committee (SC, comprising CC, CGs, SeqC, and NHGRI), such as the Practical Implementation Sustainability Model (PRISM), Reach, Effectiveness, Adoption, Implementation, Maintenance (RE-AIM), or the Consolidated Framework for Implementation Research (CFIR). Because evidence supporting the value of implementation may be limited for some of the conditions selected, the program will likely need to use an effectiveness-implementation hybrid design [PMID:22310560]. Common, standardized, patient-centered outcomes, implementation outcomes, and system metrics would be proposed and adopted by the SC. Results from this pilot program will be used to refine broader population screening programs that may involve an expanded number of conditions, screening settings, or implementation strategies. Lessons learned and successful approaches will be gathered and disseminated through outreach efforts such as conferences, publications, websites, etc.

The CGs and CC will propose conditions beyond Tier 1 to be included in the screening program, including the evidence supporting their value, workflows for testing and follow-up, education and CDS to be provided, costs, and outcome measures. They will also provide plans for community engagement in the design, conduct, and evaluation of the screening program, distinguishing aspects that may need to be adapted for their specific communities from those that can be applied more generally. They will propose and implement referral strategies for care of patients found to have risk variants and evaluate the strategies' effectiveness. The SC will agree upon a program-wide set of screening conditions and a protocol for conducting the study. All CGs will be expected to implement the same approved screening with protocols and approaches to community engagement and patient referral being adapted locally.

The program will engage PCPs to enroll, screen, and follow approximately 20,000 participants, each undergoing sequencing with only CLIA validation of a selected set of monogenic variants returned to the providers. The goal is to start with conditions that have

the strongest available evidence, recognizing that evidence might accrue over time for other conditions to mature to implementation. Each CG will be expected to have sufficient Clinical Sites (CSs) including PCPs, patient populations, and experience to offer the test and enroll 5,000 participants, complete screening, return results and implement referral and follow-up within a 24-month period. Analysis of the implementation, process, and health outcomes (limited to the 24-month period if applicable) will be conducted on the network-wide population. The SC will identify and collect implementation, process and health outcomes important to patients, clinicians, and other stakeholders for successful uptake of screening and referral to follow-up care in consultation with patients, communities, and disease experts. Outcomes should address questions such as: 1) What are the reach, uptake, acceptability, feasibility, and potential sustainability of genomic screening in primary care for patients and clinicians? 2) What are the screening conditions that are acceptable or not in different settings/communities? 3) What strategies will be necessary to facilitate equitable offering, uptake of, and action upon population screening? 4) What type of referral care is available in diverse settings and how often do patients pursue it?

The SC will devise and implement approaches for filling key gaps for the primary care workforce, including appropriate educational materials for clinicians and their patients, efficient workflows, effective referral systems, and robust informatics infrastructure and clinical decision support. All recruited patients should be receiving their care at U.S. clinical care settings. Each CG should have a broad range of available expertise in and capabilities for genomic medicine implementation, including genomic screening, prevention research, community engagement, implementation science, clinical medicine, clinical informatics, bioethics, policy, and genomic education.

Conditions to be implemented should include the three CDC Tier 1 conditions described above, along with conditions with a strong but perhaps not yet convincing evidence base. Such conditions might include *HFE* hemochromatosis, *ATTR* cardiomyopathy, *APOL1* hypertension or other conditions that investigators might propose in addition to the Tier 1 conditions. Justifications for proposed additional screening conditions should be provided, including expected prevalence, penetrance, actionability, and validity of testing. Criteria for selecting screening criteria should be proposed and agreed upon in protocol development.

As the intent of this program is to facilitate implementation of genomic screening in primary care, screening should be easily implemented in the course of patient care. The agreed-upon protocol should also emphasize interoperability of processes, standards, referral patterns, best practices, and data across sites and with external health systems as feasible.

Relationship to Ongoing Activities: This is in response to input from the scientific community collected at the GMXV meeting. It builds upon collaborative approaches developed by NHGRI's eMERGE and IGNITE networks. Its focus on primary care providers will complement the system-wide emphasis of the newly created genomics-enabled Learning Healthcare Systems (gLHS) program.

Mechanism of Support: U01 cooperative agreements

Funds Anticipated: $7M/year, 4-6 Clinical Groups, 1 Coordinating Center, 1 Sequencing Center, 5 years total.