Concept Clearance for RFA

Implementing Genomics in Practice Phase II (IGNITE II):
Pragmatic Clinical Trials in Genomic Medicine

National Advisory Council for Human Genome Research (NACHGR), May 2017

Purpose

The National Human Genome Research Institute (NHGRI) proposes two Requests for Applications (RFAs) for multi-site clinical groups and one RFA for a Coordinating Center to assess genomic medicine interventions by conducting a series of large-scale pragmatic clinical trials. Objectives of the initiative are to: 1) measure the clinical utility and cost-effectiveness of genomic medicine interventions through large, pragmatic, network-wide trials; 2) assess approaches for real-world application of genomic medicine in diverse clinical settings outside of specialized centers; and 3) produce generalizable knowledge on the types of genomic medicine interventions requiring randomized clinical trials and effective methods for conducting them.

Background

For the past six years, NHGRI's genomic medicine research programs have explored and tested appropriate uses of genomic information in clinical care through collaborative networks evaluating electronic health record (EHR)-driven phenotyping and return of genomic results, newborn and clinical genome sequencing, variant curation, and dissemination of genomic medicine approaches to diverse clinical settings outside specialized centers. It has become clear that a major barrier to large-scale genomic medicine implementation is the lack of convincing clinical evidence that would compel clinicians to adopt promising strategies and payers to pay for them. Genomic medicine interventions seem to be held to the highest evidentiary standards—randomized clinical trials—and without such trials widespread adoption is unlikely to occur. While extrapolation from observational data to effective clinical implementation in genomic medicine may be less prone to bias than other interventions, few trials have been conducted to permit comparison of observational and trial data.

IGNITE Phase I was funded in 2013 and 2014 (RFA-HG-12-006, 12-007, and 13-004) to assess and disseminate methods for effective implementation and sustainability of genomic medicine in diverse clinical settings. The resulting consortium included 6 networked groups involving a lead site and multiple "partner" sites in varied settings such as minority-serving hospitals, community health centers, and military and VA hospitals. Each of the 6 groups implemented a unique genomic medicine intervention involving pharmacogenomics, molecularly targeted therapy, or complex disease management. The 6 originally funded groups have expanded from having 111 partner sites to 272 partner and 11 affiliate sites throughout the U.S.

The value of a network approach for collaborative implementation research was recently demonstrated in an analysis of ~1800 patients undergoing percutaneous coronary intervention (PCI) and *CYP2C19* clinical genotyping at 7 IGNITE sites and affiliates. These data showed that risk of major adverse cardiovascular events more than doubles in post-PCI patients carrying a *CYP2C19* loss-of-function allele who received clopidogrel compared to those who received alternative antiplatelet therapy, but subtle biases in selecting patients for genotyping and following them for adverse events are possible in such observational, non-randomized data. Extending such collaborative efforts to network-wide clinical trials was highlighted in the IGNITE and Beyond workshop (see below) as a major opportunity for rapid and efficient evidence generation for genomic medicine implementation.

IGNITE I was designed to address substantial skepticism that genomic medicine could be disseminated effectively from highly specialized centers into resource-limited settings and underserved populations. IGNITE projects such as GUARDD, which incorporates *APOL1* risk information in the care of African-American hypertensives to prevent renal disease, showed the effectiveness and community acceptance of a streamlined approach to genetic counseling that was needed to transfer the intervention from Manhattan's Mount Sinai Medical Center to resource-limited community health clinics in Harlem and the Bronx.

In August 2016, IGNITE investigators held a workshop that identified key opportunities for increasing stakeholder support of genomic medicine, such as involving representatives from health insurance and biotechnology companies in study design and evaluation of cost benefits. NHGRI subsequently held the "IGNITE and Beyond" workshop to identify optimal study designs for future genomic medicine implementation program(s). The workshop recommendations to foster more robust collaboration between academic and community centers, include racial and ethnic minority populations, and conduct large, network-wide trials addressing clinical outcomes are reflected in this proposal for IGNITE Phase II.

Research Scope and Objectives

IGNITE II aims to support a Network of multi-site Clinical Groups (CGs) involving diverse settings and populations to conduct pragmatic clinical trials of genomic medicine interventions. Pragmatic clinical trials (PCTs) allow the use of flexible protocols to evaluate efficacy in real-life clinical settings and to produce results that can be generalized to routine practice settings. IGNITE II will support 4-6 multi-site CGs and one Coordinating Center (CC) to adapt, expand, and implement 2-4 network-wide PCTs. Each CG application will propose one trial to test a genomic medicine intervention that: 1) has evidence of feasibility in prior studies, 2) addresses clinically important outcomes achievable within 1 year of randomization, and 3) is adaptable to a wide range of clinical settings. Suitable research topics include (but are not limited to) pharmacogenomics-based drug prescribing, risk reduction in genetically-defined high-risk individuals, and early genomic-based diagnosis in critically ill newborns. Proposed trials should include assessments of approaches for real world applications and provide generalizable knowledge about the use of PCTs in genomic medicine. Applicants will be asked to include a plan for comparing results of each trial to existing non-interventional studies in order to identify potential biases affecting the generalization of observational data to clinical practice. Applicants will be encouraged to discuss proposed trials with NHGRI staff prior to submission.

Each CG will be expected to involve multiple sites with a proven record in recruitment, retention, and evaluation of genomic medicine implementation studies in diverse clinical settings and populations. Inclusion of at least 50% of patients from diverse clinical settings such as community hospitals, family medicine or primary care practices, and at least 35% enrollment from racial and ethnic minority populations will be expected. A second RFA will solicit CGs with at least 75% enrollment from racial and ethnic minority populations.

In addition, each CG will propose one Network-wide research study related to ethical, legal and social implications (ELSI) of implementing genomic medicine interventions in diverse clinical settings and populations. Topics could include an assessment of outcomes of importance to patients, clinicians or communities, or comparison of implementation strategies across the Network to identify potential barriers and solutions in different communities and settings.

Proposed Network-wide protocols passing peer review will be prioritized after award by a Protocol Review Committee (PRC) involving experts in genomic medicine, ELSI research, and clinical trials as well as relevant stakeholders. The Steering Committee, comprising the Principal

Investigators of each CG, the CC PI, and NHGRI staff, will then adapt prioritized protocols for expansion across the IGNITE II Network. Trials should be powered to detect clinically meaningful differences in outcomes within a 3-4-year recruitment, intervention, and follow-up period. In the clopidogrel example above, a trial to assess adverse events during antiplatelet treatment guided by pre-emptive genetic testing would require ~2,650 participants in the intervention arm and an equal number of controls to provide 80% power to detect a 25% risk reduction, assuming a risk allele frequency of 30% and adverse event rate of 25% in at-risk individuals. Alternatively, a study of genetic testing to increase the proportion of patients and family members with familial hypercholesterolemia placed on high-intensity statin therapy would require 3,675 patients to detect a doubling of treatment rates, and 12,500 patients to detect a 50% increase. As currently budgeted, IGNITE II could include ~15,000 patients, allowing for 2-3 large trials with some overlap in patients and several smaller studies or subgroup analyses.

To minimize cost and maximize generalizability, IGNITE II will utilize a novel funding mechanism proven effective in similar pragmatic clinical trial networks in other Institutes, including the ARDSNet, PCGC, and NIH Collaboratory. CGs will initially be funded at ~$250K direct costs/yr for 5 years, with NACHGR-approved multi-year supplements provided for participation in selected protocols. Each CG will be expected to participate in at least 2 Network-wide trials. IGNITE II will consist of 3 phases over a 5-year period. Phase I (6-12 months) will include protocol prioritization by the PRC and approval by NHGRI, protocol adaptation for Network-wide implementation by the Steering Committee, and IRB approvals. Phase II (3-4 years) will include enrollment, intervention, and follow-up. Phase III (6-12 months) will involve collaborative analysis and results dissemination. Trials will follow NIH guidelines for reporting and monitoring.

IGNITE II CG applications should include: 1) a genomic medicine intervention protocol with preliminary evidence of improved health outcomes and cost effectiveness; 2) an ELSI research protocol related to implementing genomic medicine in diverse populations and clinical settings; 3) a plan to expand the proposed protocols Network-wide; 4) demonstrated ability to implement agreed-upon Network-wide protocols, including availability of specialized care; 5) evidence of institutional support and success in participant recruitment and retention, particularly among diverse participants and settings; 6) demonstrated ability to recruit at least 3,000 patients, including at least 35% or 75% racial and ethnic minority patients depending on the RFA and at least 50% diverse practice settings; 7) a plan for genomic testing in a CLIA-certified testing environment and efficient workflow for extracting EHR information, integrating and reporting genomic results, and harmonizing clinical decision support across clinical sites.

The IGNITE II CC will participate in the development of the Network infrastructure, assist with adaptation of protocols, develop a manual of operations for each protocol, receive and disseminate weekly recruitment and monitoring reports, and assist in analysis and publication.

Mechanism of Support

These RFAs will use the cooperative agreement award mechanism; the activity code is to be determined. Anticipated duration of the program is 5 years, starting in FY18.

Funds Available

NHGRI would commit approximately $7.4M/yr for 5 years, including a $375K/yr contribution from NHGRI's ELSI research program, to support 4-6 CGs each comprising multiple clinical sites, and a Network Coordinating Center. Support would be sought from other NIH Institutes/ Centers, with priority given to scientifically meritorious projects where co-funding is proposed.

- Clinical groups: 4-6 awards, up to $1M/yr including supplements for adopted protocols
- Coordinating Center: 1 award, up to $1M/yr