Revised Concept Clearance for RFA

Clinically Relevant Variants Resource: A Unified Approach for Identifying Genetic Variants for Clinical Use

NHGRI Advisory Council, May 2012

Purpose

The National Human Genome Research Institute (NHGRI) proposes to support a process for the identification and dissemination of consensus information on genetic variants relevant for clinical care. The goals of this initiative are to: 1) identify genetic variants with likely implications for clinical care and incorporate these variants and their supporting evidence into a resource that can serve as the substrate for development of practice guidelines by relevant professional societies and other stakeholders; 2) establish a process for transferring this information to appropriate clinical organizations for development of these guidelines; and 3) engage, coordinate and build upon existing programs and reduce duplicative efforts to identify such variants across numerous research and clinical organizations. NHGRI recognizes the importance of collaborating with relevant professional organizations on this effort, such as the American College of Medical Genetics (ACMG), the Association for Molecular Pathology (AMP), the American Society of Human Genetics (ASHG), and the College of American Pathologists (CAP) and is engaging other organizations as well.

Background

Genomic studies are increasingly identifying genetic variants with potential implications for clinical care, such as variants increasing risk of disease (e.g., mismatch repair mutations in colorectal cancer) or affecting response to a drug (e.g., *CYP2C19*2* in persons receiving clopidogrel). Dozens of medical centers and research programs nationwide are beginning to explore the use of such variants in clinical care, and many are developing approaches for identifying variants to be assayed and the actions to be recommended when they are detected. In most cases, each is evaluating the same assays, reviewing the same literature, and assessing the same evidence. In addition, major efforts to identify variants relevant to drug response have been ongoing through the NIGMS-led Pharmacogenomics Knowledge Base (PharmGKB) and Pharmacogenomics Research Network (PGRN) for some years.

A unified approach to harness and coordinate these often isolated, individual deliberative efforts and disseminate their findings would reduce wasteful duplication of effort and speed adoption of actionable genetic findings for use in clinical care. Relevant information could be reviewed and synthesized once (and appropriately revisited over time) by experts nominated by relevant professional societies and agencies, using an agreed-upon consensus framework and incorporated into a user-friendly and accessible resource. These evidence syntheses and consensus findings can then be handed off to appropriate professional organizations for development of practice guidelines, to be considered for implementation at the level of a given institution, in the context of local practice and community preference to improve patient care. A framework for evaluating and recommending variants for implementation, appropriately tailored to the risks and benefits of the clinical action proposed, could be disseminated for consideration

by other health systems. Such decisions, if effectively captured and indexed, could also draw upon and contribute to the extensive research activity in return of genomic research results supported by NHGRI and other NIH Institutes.

Such an effort could also build on extensive work to identify and catalog genotype-phenotype associations with potential clinical implications. Close integration with these ongoing efforts would position this consensus project at the nexus of variant discovery as captured by these databases, and decision-making for reporting results, as addressed by ongoing research activities and appropriate professional organizations. Given the large number of groups currently undertaking such efforts, a multi-institutional approach that involves and engages these ongoing efforts and ensures that diverse perspectives are sought and considered, is most likely to yield a widely-embraced and influential resource.

An effective dissemination strategy is a key component of such a resource, to ensure that it is accessed and applied. Maximizing the usefulness of the resource will require strategies tailored to the numerous constituencies likely to consult it, including professional organizations, regulatory agencies, payers, medical institutions, clinicians, researchers, and possibly even patients and the lay public. Close consultation with these constituencies and responsiveness to their needs will be essential to the success of the program, with guidance and facilitation by the NHGRI, other NIH Institutes, and appropriate professional organizations. The framework for developing consensus can also be distributed for other health systems, especially non-US systems, to consider and adapt as desired.

This initiative will support the development and operation of a consensus process for identifying potentially actionable variants and disseminating that information to clinicians and investigators.

Research Scope and Objectives

This RFA would support a single awardee, with the close involvement of NHGRI and other collaborators such as ACMG, AMP, ASHG, and CAP and a jointly-appointed expert Steering Committee, to collect, extract, and evaluate the clinical relevance of genetic variants associated with clinically important traits and synthesize these data into a user-friendly resource. Applicants would develop and propose approaches for a multi-component strategy, including engagement and integration with ongoing efforts, data synthesis and curation, consensus development, hand-off to clinical organizations for development of practice guidelines, and dissemination.

Data synthesis and curation would be expected to involve distilling and integrating information from relevant databases and resources, such as ClinVar, eMERGE, and PharmGKB, into a data resource, and updating the resource as needed. The consensus process would be expected to include identifying clinical groups, research programs, and relevant professional organizations currently conducting such efforts, and soliciting their advice and participation; developing a framework for the review and evaluation process; defining domains into which variants might be grouped (e.g., cardiovascular disease, cancer, etc.); and applying the review framework, adapted as needed to the specific domain, to reach consensus on the variants to be included in the resource. Applicants would be expected to propose approaches for bringing the deliberations to a consensus, or for dealing with the inability to do so, and for obtaining input on draft recommendations from relevant professional organizations and agencies. Proposed

approaches would also be expected to ensure consistency of domain-specific recommendations with the established framework and with products of other domains.

Dissemination would involve providing consensus findings on a set of potentially actionable genetic variants and the actions that should be considered, with supporting evidence and documentation of the consensus process. Applicants would be expected to survey ongoing efforts in consensus development regarding variants for clinical implementation, as well as the ethical, legal, social, and policy issues regarding results reporting, and to propose approaches for integrating with and building upon them. This will enhance coordination with other efforts supported by NIH and other organizations, avoid duplication, and sufficiently circumscribe the effort to be practical within a reasonable timeframe and budget. Importantly, the awardee will not address *screening* recommendations, which are typically matters of health care policy and economics as well as scientific evidence, but will provide the evidence on which screening recommendations could be made.

Applicants would be expected to describe their approaches for engaging and involving the numerous ongoing efforts in identifying clinically relevant genomic variants and for encouraging recognition and acceptance of the resulting consensus process. Expertise needed and sought for the Steering Committee, and plans for ensuring a diversity of perspectives while recognizing the need for ultimate consensus in a time-limited and efficient process, should also be described. Willingness to accept guidance and assistance from NHGRI, in close consultation with other relevant stakeholders, and potential reasons for inability to do so, would also be described. Applicants would be expected to describe their approaches for defining and prioritizing domains into which variants might be grouped for review and evaluation, sifting the published literature and data resources for genes and variants for consideration, gathering the available evidence regarding their clinical impact and effects of potential interventions, developing consensus, obtaining feedback, and handing the conclusions off to appropriate professional organizations for guideline development. Approaches for grouping genes or variants into those likely ready for implementation, those clearly having no clinical implications, and an intermediate group for which more information is needed should be described. Plans for dealing with a profusion of variants of unknown significance, particularly as identified from genomic sequencing, and for focusing on particular types of variants or genes as at least an initial, manageable approach, would also be expected.

Mechanism of Support

This RFA would use the NIH U01 (Cooperative Agreement) award mechanism. Anticipated duration of the program is four years, with two to three domains addressed in the first year and five to eight domains per year thereafter. Effective development and increasing use of the resource would prompt consideration of renewing support for it so long as the need remained.

Funds Available

NHGRI would commit approximately $2M in FY13 and $4M per year for the subsequent three years for up to 20 domains. Support would be sought from other NIH Institutes, and consideration would be given to elevating priority for moderate-priority domains where co-funding is proposed.