Concept Clearance for RFA

ClinAction: Unifying Efforts to Identify Potentially Actionable Genetic Variants

NHGRI Advisory Council, February 2012

Purpose

The National Human Genome Research Institute (NHGRI) proposes to support identification and dissemination of consensus information on potentially actionable genetic variants in clinical care. The goals of this initiative are to: 1) identify, from existing databases, genetic variants with implications for clinical care and disseminate this information and supporting evidence; 2) develop clinical decision support systems for incorporating these variants into clinical care; and 3) build upon existing programs, unify approaches, where appropriate, and reduce duplicative efforts to identify such variants across numerous research and clinical organizations.

Background

Genomic studies are increasingly identifying genetic variants with potential implications for clinical care, such as variants increasing risk of disease (mismatch repair mutations in colorectal cancer) or affecting response to a drug (*CYP2C19*2* in persons receiving clopidogrel). Dozens of medical centers nationwide are beginning to explore the use of such variants in clinical care, and several have implemented pilot programs for genotyping one or a few variants and using that information in clinical decisions. Each of these centers has had to develop its own approaches for identifying the variants to be assayed and the actions to be recommended when they are detected. Each is evaluating the same assays, reviewing the same literature, and assessing the same evidence, and for the most part identifying the same variants for possible clinical use. Though none has yet identified more than a handful of such variants, the growing knowledge base and increased use of sequencing and functional studies are poised to yield a host of variants for possible clinical action. 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 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 agreed-upon criteria, to produce consensus recommendations. These recommendations could then be considered for implementation at the level of a given institution, in the context of local practice and community preference. 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 Institutes in programs such as the Return of Results Consortium (RFAs HG-11-003 and HG-11-004), Clinical Exploratory Sequencing Centers (RFA HG-10-017),

Electronic Medical Records and Genomics Network (RFAs HG-10-009, HG-10-010, and HG-11-022), and PGRN's Clinical Pharmacogenetics Implementation Consortium.

Such an effort could also build on extensive work to identify and catalog genotype-phenotype associations with potential clinical implications, such as the nascent ClinVar database of the National Center for Biotechnology Information (NCBI) [www.ncbi.nlm.nih.gov/clinvar/], the International Standards for Cytogenomic Arrays (ISCA) database [www.iscaconsortium.org], the FDA's Pharmacogenomic Biomarkers in Drug Labels [www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm], PharmGKB's Very Important Pharmacogenes [www.pharmgkb.org/search/annotateGene/], and CDC's Evaluation of Genomic Applications in Practice and Prevention [www.cdc.gov/genomics/gtesting/EGAPP/recommend/]. 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 the programs described above. This will facilitate a sharper focus on the expertise and approaches needed to weigh genomic and clinical information in identifying potential clinical actionability while integrating with other key aspects.

The need for such a consensus process has been widely recognized, starting from the first efforts to consider returning genetic results obtained in the course of population-based research, such as the 2004 NHLBI Working Group on Reporting Genetic Results in Research Studies. Development of such a process was strongly recommended in consultations with other Institutes by NHGRI's Disease-Oriented Genomic Medicine Working Group; at two follow-up NHLBI working groups in 2009 and 2011; at NHGRI's two Genomic Medicine meetings in June and December 2011 (www.genome.gov/27546373); and at the December 2011 Characterizing and Displaying Genetic Variants for Clinical Action Workshop (www.genome.gov/27546581).

An effective dissemination strategy is a key component of such a resource, to ensure that it is accessed and used. Implementation of consensus recommendations at individual institutions, after appropriate consideration of local practice patterns and community needs, can be facilitated by providing suitable clinical decision support rules (that is, algorithm descriptions) or tools (actual software programs or other materials) for modification and adoption at the point of care. User-friendly tools for clinicians without access to sophisticated systems will also increase the reach and use of the resource. The consensus framework 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 to collect, extract, and evaluate the clinical relevance of genetic variants associated with clinically important traits, and to recommend them and potential actions if they are detected, for consideration for use in clinical care. Applicants would develop and propose their own approaches for a multicomponent approach including synthesis, curation, consensus development, integration with ongoing efforts, 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 ClinAction 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 for review and evaluation (cardiovascular disease, cancer, etc.); and applying the review framework, adapted as needed to the specific domain, to reach consensus on variants and actions to be recommended. Applicants would be expected to propose approaches for bringing the deliberations to a consensus, or for dealing with inability to do so, and for obtaining input on draft recommendations from relevant professional organizations and agencies. Proposed approaches would also be expected for ensuring consistency of domain-specific recommendations with the established framework and with products of other domains.

Dissemination would involve providing consensus recommendations on actionable variants and actions that should be considered, with supporting evidence and documentation of the consensus process. Applicants would be expected to propose a process for developing and distributing clinical decision support rules and tools for adoption in EMRs and other clinical systems, as well as user-friendly tools for clinicians without access to such systems. 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. The emphasis will not be on whether clinicians should be advised to *order* a particular assay, but on what could or should be considered if a patient's genetic results were already *available* (through research studies, commercial or direct to consumer genetic testing, etc).

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.