National Advisory Council for Human Genome Research

February 8, 2016

Concept Clearance: Clinical Sequencing Evidence-Generating Research (CSER2)

Purpose:

NHGRI proposes 3 Requests for Application (RFAs) for a Clinical Sequencing Evidence-Generating Research Program (CSER2), based on the successful pilot-style work of the Clinical Sequencing Exploratory Research (CSER) program. CSER2 will: 1) generate and analyze evidence to further investigate the clinical utility of genome sequencing in multiple clinical contexts; 2) research the critical interactions among patients, family members, health practitioners, and clinical laboratories to better inform implementation of the clinical genome sequencing process; and 3) investigate the feasibility of exchanging genomic, clinical, and health utilization data within existing healthcare systems to build a shared evidence base for clinical decision-making. CSER2 will not only focus on accelerating the diagnostic process, but will also investigate what is effective in improving outcomes and patient care, and why. To ensure the effective utilization of CSER2-generated evidence for the establishment of implementation and reimbursement policies, CSER2 will refine evidence measures and collaborate with professional societies, patients, payers, and regulatory agencies. To broaden the applicability of the evidence it generates, CSER2 will emphasize the inclusion of diverse populations, i.e., populations that experience health disparities (including racially and ethnically diverse populations) and populations that receive clinical care outside of specialized academic medical centers.

Background:

CSER (RFA HG-10-017) was funded in 2011 to explore the use of genome sequencing in clinical care and to identify associated challenges and opportunities in a variety of clinical contexts (e.g., pre-conception screening, pediatrics, cancer, and healthy adults) at six clinical sites. The large number of meritorious applications and added value of varied clinical contexts led to later funding three additional clinical sites and a Coordinating Center and integrating investigator-initiated grants related to the return of genomic results and the NHGRI Intramural ClinSeq project. CSER has recruited 5200 participants and demonstrated the feasibility of implementing a clinical workflow that: recruits, consents, and educates patients and providers; generates, interprets, and returns relevant genomic information; and investigates related ethical, legal, and social issues (ELSI). CSER has disseminated widely applicable best practices including models for genomics-oriented informed consent tailored to the clinical setting, models to improve the consistency of genomic variant interpretation, and approaches to the disclosure of primary pediatric and tumor findings and secondary findings more broadly. Collaborating with the Electronic Medical Records and Genomics (eMERGE) network, CSER also identified barriers and recommended approaches to incorporating genomic information in electronic health records. CSER's impact on the development and refinement of clinical guidelines included co-leading and contributing gene-annotation resources to three sets of ACMG recommendations (on secondary findings, variant interpretation, and clinical laboratory standards) and initiating studies to assess real-world application of these guidelines.

In prioritizing opportunities for clinical genome-sequencing research, NHGRI sought wide input in a series of workshops: *Future Opportunities for Genome Sequencing and Beyond, Genomic Medicine VIII Workshop*, and *Integrating Genomic Sequencing into Clinical Care: CSER and Beyond.* The scope and objectives of CSER2 outlined below reflect several of the

highest priority recommendations from these workshops that CSER2 is uniquely poised to address, as a natural follow-on from CSER's dedicated focus on the clinical encounter and interactions among patients/family members, practitioners, and laboratories.

Relationship to Ongoing Activities:

CSER, ClinGen, IGNITE, eMERGE, and NSIGHT represent the key components of NHGRI's extramural genomic medicine portfolio. NHGRI also plays a major leadership role in the Common Fund's Undiagnosed Diseases Network (UDN). EMERGE and UDN have primary emphases on penetrance of actionable genomic variants and undiagnosed diseases, respectively, and IGNITE studies the implementation of genomic tests with established clinical utility. CSER2, by contrast, emphasizes determining the clinical utility of genome sequencing in varied real-world clinical contexts and settings. Its focus on the clinical workflow and on the technical and ELSI issues raised in the clinical encounter will provide unique and critical information on how existing approaches to informed consent, genomic variant interpretation, and results disclosure can best be used in, and tailored to a range of patients, practitioners, and clinical laboratories. The program's close integration with clinical laboratories will generate genomic variant interpretations and case-level data useful for ClinGen and related programs to further improve annotation of clinically relevant variants. As was true for collaborations between CSER and eMERGE, CSER2 interactions with other genomic medicine programs will be synergistic and not duplicative.

Proposed Scope and Objectives:

CSER2 will comprise between 7 and 11 clinical sites and a Coordinating Center. A separate investigator-initiated effort, described in the accompanying document, will also be issued. Clinical sites will determine the clinical utility of genome sequencing in multiple clinical contexts, as defined by disease or other clinical or demographic factors, by studying at least 10,000 ancestrally, clinically, and socioeconomically diverse participants (e.g., patients and family members) across sites over the 4-year project period. In contrast to CSER, which primarily studied participants with whole exome or genome sequencing (WES/WGS), each CSER2 clinical site will evaluate clinical utility measures for a comparison group (e.g., participants sequenced for gene panels) as well as a WES/WGS group. Adopting ACMG's definition of clinical utility, a consensus set of evidence measures for clinical utility will be identified and implemented. By using standardized measures, the >10,000 participants across CSER2 provide a large sample of diverse participants, clinical settings, and care settings that can be used for consortium-wide analyses, including sub-group analyses. Integrating genomic, clinical, and healthcare utilization data, CSER2 will draw on varied clinical contexts to investigate health system-wide impact of genomic technologies where clinical utility has yet to be established, yet also allow the study of rarer outcomes or smaller effect sizes.

CSER2 will also focus on research at the intersection of patients and family members, health practitioners, and clinical laboratories, with ELSI research integrated throughout. Examples of research opportunities include assessing how best to: 1) conduct patient-centered recruitment (e.g., compare the responsiveness of practitioners to patient preferences, particularly in underserved settings); 2) characterize the 'cascade' of genomic information (e.g., assess how patient-centered outcomes impact family members and understand how to incorporate this information into clinical utility or healthcare utilization analyses); 3) reanalyze existing genomic data (e.g., determine whether considering multiple factors such as patient-centered utility, patient- or provider-reported phenotype information and updated genomic variant interpretation data impacts outcomes); 4) tailor genomic variant interpretation and disclosure of genomic results (e.g., study patient/family-practitioner

communication as well as practitioner-laboratory interactions); 5) examine ELSI issues, with a particular focus on those arising uniquely in diverse populations or in settings outside of academic medical centers.

Genomic, clinical, and healthcare utilization data tend to exist in siloes within healthcare systems, and facile data exchange is needed to increase the utility of genome sequencing in clinical care. Each CSER2 site will investigate the feasibility of exchanging these data types within its healthcare system(s) to build a shared evidence base for clinical decision-making. While CSER2 will continue to share genome sequence and variant interpretation data with dbGaP and ClinVar, it will also pilot the exchange of multiple data sources within a healthcare system using a real-world, "effectiveness" approach. This approach will enable CSER2 to assess iteratively whether genomic sequencing data lead to improved patient diagnosis, treatment decisions or outcomes, or information that might subsequently benefit other patients with similar genomic variants and findings.

The research described above will inform policies regarding the regulation of and reimbursement for genome sequencing in clinical practice. For example, CSER2 data on test accuracy, clinical utility and healthcare utilization will address high-priority regulatory science areas and could contribute to evidentiary frameworks used by professional societies and payers. Recognizing that CSER2 data are likely to inform decision-making related to the adoption of genome sequencing for clinical care, CSER2 will work with stakeholders in their roles as co-investigators, liaisons, or other positions to identify and apply evidence measures, respond to emerging needs for evidence, and accelerate the adoption of genome sequencing approaches demonstrated to have clinical utility.

All clinical sites will be strongly encouraged to recruit participants from diverse populations, as defined in the Purpose section above. Separate RFAs for two types of clinical sites will be issued: one for clinical sites recruiting >25% of participants from diverse populations, and another for clinical sites with enhanced diversity that will adhere to the same clinical site aims with expected recruitment of >60% of patients from diverse populations. All clinical sites will address one or more diversity-related research topics: 1) unique challenges associated with disclosure and interpretation of genomic information; 2) differences in disease-related presentation, diagnosis, treatment, or healthcare utilization; 3) novel methods for healthcare delivery; or 4) other relevant areas. Partnerships with existing efforts will be encouraged to meet the diversity and clinical aims of the RFAs. Stakeholder engagement in both types of sites will enhance effective translation of clinical discoveries in settings where they are most needed.

A separate RFA will be issued for a CSER2 Coordinating Center (CC) to facilitate interactions among sites, convene required meetings of the Steering Committee and Working Groups, and accelerate the completion of CSER2 goals. The CC will coordinate cross-study interactions and disseminate findings and best practices. Complementing site-specific outreach, the CC will coordinate and facilitate CSER2-wide community outreach, stakeholder engagement, and interactions with other NHGRI programs such as eMERGE and IGNITE.

Mechanism of Support and Funds Anticipated:

NHGRI will commit roughly $21.8M/yr for FY17-FY20 to three RFAs, as follows:

- Clinical sites (UM1): up to $16.1M (5-7 awards, $11.5M-$16.1M)
- Clinical sites with enhanced diversity (UM1): up to $11.2M (2-4 awards, $5.6M-$11.2M)
- Coordinating Center (U01): 1 award, up to $1M per year