National Advisory Council for Human Genome Research

February 8, 2016

Concept Clearance: Investigator-Initiated Clinical Sequencing Research (iCSR)

Purpose:

NHGRI proposes a Program Announcement with Set-aside funds (PAS) and a Program Announcement with Review (PAR) for Investigator-Initiated Clinical Sequencing Research (iCSR) as a companion to the three Requests for Applications (RFAs) for the Clinical Sequencing Evidence-generating Research Program (CSER2). Complementing the consortium-wide scientific aims specified in the CSER2 concept, this parallel investigator-initiated component would stimulate innovation and rapid progress by funding individual investigator groups to address scientific research in targeted areas related to clinical genome sequencing, including: 1) studies that enhance our understanding of whether and how clinical sequencing impacts disease diagnosis and treatment; 2) development of bioinformatic and analytic approaches to integrate multiple data types to improve identification and interpretation of genomic variants and the use of this genomic information in clinical settings; 3) investigation of the function of putative pathogenic genomic variants identified in CSER and CSER2. Investigator-initiated Ethical, Legal Social Implications (ELSI) research related to CSER2 will continue to be supported under HG PAs-14-276 (R01), 14-277 (R03), and 14-278 (R21), and will not be supported by this PAS/PAR.

Background:

The Clinical Sequencing Exploratory Research (CSER) program (RFAs HG-10-017 and 12-009) was funded in 2011 to explore the use of genome sequencing in clinical care and to identify associated challenges and opportunities across a variety of clinical settings. It also successfully integrated a series of R01 and R21 grants (RFAs HG-11-003 and 11-004) funded in 2011 by NHGRI's ELSI Research Program on returning genomic research results to participants in genomic studies, as well as the NHGRI Intramural ClinSeq project. Studying varied clinical contexts (e.g., pre-conception screening, pediatrics, cancer, and healthy adults), CSER has recruited 5200 patients, yielded sequencing findings contributing to diagnosis in 15-40% (depending on the clinical setting), and identified secondary or incidental genomic findings in 4-5% of participants.

Throughout its course, CSER has generated intriguing findings, many of which are poised for further investigation by smaller teams of independent investigators. Examples include:

- Heterogeneity of diagnostic yield has been observed across diseases (higher for neurologic and retinal conditions, for example, and lower in cardiology and dysmorphology), suggesting that clinical sequencing efforts could be targeted at conditions more likely to yield identifiable underlying pathogenic variants.
- Heterogeneity of phenotypic manifestations of known pathogenic variants has been observed among family members, including relatives who are homozygous for variants associated with severe Mendelian conditions in whom subtle findings may have been overlooked. These observations suggest a much broader spectrum of diseases potentially caused by specific genomic variants.
- Heterogeneity in the genotypic and phenotypic spectrum of disease suggests there may be underlying person-specific factors influencing the manifestation of disease.

- Integration of transcriptomic data in CSER pediatric cancer patients has changed patient management and improved outcomes; innovative methods are thus needed to combine –omic data such as transcriptomics and epigenomics with genome sequence and clinical data in clinical research and patient care.
- Substantial informatics barriers to incorporating genome-sequence data into electronic medical records and clinical decision-support tools are impeding the full integration of genomic information into clinical care at CSER sites.
- Heterogeneity in interpreting and classifying variant pathogenicity across clinical laboratories (as demonstrated in a CSER "bake-off") suggests differences not only in the databases being consulted but also in the individual interpretation of different types of source information.
- Numerous pathogenic variants have been identified in CSER to date and are expected in CSER2; functional characterization of such variants could suggest valuable diagnostic or therapeutic pathways.
- Multiple variants have been strongly but not conclusively linked to disease in CSER and more are expected in CSER2; functional studies could facilitate interpretation and classification of these variants.

In addition to these CSER research findings, related recommendations suitable for investigator-initiated research in clinical genome sequencing were identified in NHGRI's recent workshops on *Future Opportunities for Genome Sequencing and Beyond*, *Genomic Medicine VIII*, and *Integrating Genomic Sequencing into Clinical Care: CSER and Beyond* Together, these form the basis for the topics suggested for investigation in the "Proposed Scope and Objectives" section.

Proposed Scope and Objectives:

iCSR is expected to build upon and complement the work of the companion CSER2 RFA program through targeted projects pursuing innovative, focused research questions raised by or relevant to CSER and CSER2 as described above. Application of novel concepts, approaches, methodologies, and/or instrumentation to these questions will be encouraged. Applicants should describe the generalizability and broader relevance of the proposed research to clinical sequencing in settings beyond the targeted genes or diseases included in their specific proposal. Applicants should also clarify how their proposed work will impact our understanding of disease diagnosis and treatment. A list of genomic variants identified in CSER will be made available with the release of the RFA, and will be updated based on findings from CSER2. Projects focused solely on variant discovery will be considered unresponsive. Topics suitable for this PAS/PAR include but are not limited to:

- Targeted investigation of diseases for which genome sequencing confers a high diagnostic yield that enhance our general understanding of whether and how genome sequencing contributes to disease diagnosis and treatment
- Examination of factors influencing the phenotypic spectrum of genomic variants identified in CSER and CSER2, such as age or developmental stage, treatment, co-existing illness, and other modifiers
- Addition of family history to large-scale sequencing efforts to determine when family history adds to or is more useful than sequence information
- Development of computational and health-economic approaches to identifying characteristics of diseases likely to derive the greatest value from clinical genome sequencing
- Improvement of methods to integrate existing clinical data (including genomic data) from heterogeneous sources in electronic medical records and decision-support tools

- Integration of other data types, such as environmental data or –omics data (e.g., transcriptomics, epigenomics, etc), to improve assessment of clinical validity for variants identified through clinical sequencing efforts
- Development of novel models for annotating and interpreting existing functional data to improve interpretation of genomic variants for clinical use
- Interpretation and elucidation of function of pathogenic and likely pathogenic genomic variants identified in CSER and CSER2

Applicants to this PAS/PAR are expected to come from institutions outside of the funded CSER2 sites; awards will not be made to the same applicants, including PIs, key personnel, or institutions in iCSR and CSER2. iCSR will address key research questions that require small, rapidly responsive, and nimble research settings rather than the substantial clinical genome sequencing infrastructure and consortium-wide approach needed for CSER2. Applicants for iCSR will be encouraged to collaborate with CSER and CSER2 awardees either in developing their applications or after awards are made, as appropriate to the science proposed. Awardees will be invited, but not required, to participate in CSER2-wide consortium meetings and working groups, as relevant to their projects. Attendance at an annual iCSR grantees meeting to present and discuss their findings will be required, and may be held in conjunction with CSER2 meetings.

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). This investigator-initiated program will complement the consortia-based work in these programs, most specifically CSER2. Applications addressing the function of putative pathogenic genomic variants will begin to explore the ability to bridge the gap between basic and clinical research as recommended in the Genomic Medicine VIII workshop. This issue will be explored further in Genomic Medicine IX in April 2016, and the deliberations of that meeting will be available to applicants for this PAS/PAR. As noted above, ELSI-focused research applications are expected to apply under the existing program announcements of NHGRI's ELSI Research Program.

Mechanism of Support:

R01 Research Project Grants solicited through a Program Announcement with Set-aside Funds (PAS) and R43/R44 Small Business Innovation Research (SBIR) Grants solicited through a Program Announcement with Review (PAR).

Funds Anticipated:

NHGRI will commit roughly $3 M/yr for FY17-FY20, for up to 6 awards, each with <$300K direct costs/yr (~$500K/yr total costs) for four years.

Each R43/R44 is expected to be $150,000 for Phase I awards and $1,000,000 for Phase II awards, with higher amounts allowed, if well justified. Funding for R43/R44 would come from the SBIR/STTR set-aside.