Concept Clearance for RFA (U19)

Genomic Sequencing and Newborn Screening Disorders

National Advisory Council for Human Genome Research, May 2012

Purpose

The National Human Genome Research Institute (NHGRI) and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) propose an RFA to explore the implications, challenges and opportunities associated with the possible use of genomic sequence information in the newborn period. The goals of this initiative are to stimulate research in three coordinated areas specifically applicable to newborn screening: 1) acquisition and analysis of genomic datasets that expand considerably the scale of data available for analysis in the newborn period; 2) clinical research that will advance understanding of specific disorders identified via newborn screening through promising new DNA-based analysis; and 3) research related to the ethical, legal and social implications (ELSI) of the possible implementation of genomic sequencing of newborns.

Background

Newborn screening programs currently screen more than 4 million U.S. infants per year, making them the most common form of genetic testing (testing of DNA or gene products) performed in the United States. This public health program has affected countless lives through identification of infants at risk for congenital disorders for which early interventions and treatments have the potential to reduce morbidity and mortality. The disorders most often included in state newborn screening panels are based on the Recommended Uniform Screening Panel as reviewed and adopted by the Secretary of Health and Human Services.

Traditionally, DNA-based testing has not been a primary newborn screening methodology but has been used for second-tier confirmation of the diagnosis for many newborn screening disorders for which molecular testing is available (e.g., cystic fibrosis). Genomic technologies have advanced dramatically over the past decade, however, to the point where the prospect of incorporating individuals' whole genome sequence information into their medical care is under serious discussion and careful study. Over the next several years, genome sequencing of large numbers of individuals and application of that information in the context of specific clinical studies and ongoing medical care are expected to increase the clinical utility of whole genome data substantially. At the same time, the costs of collecting and interpreting genome data are falling below the costs of conducting some individual genetic tests. These new, sophisticated and increasingly cost-effective techniques for DNA-based sequencing and analysis may make it possible to expand newborn screening and substantially enhance its clinical and public health value. Recognizing these trends, NHGRI and NICHD held a workshop in December 2010 to identify elements of a trans-NIH research agenda that could inform the possible application of new genomics concepts and technologies to newborn screening and child health.

Research Scope and Objectives

This RFA would support up to five pilot studies to collect comprehensive genomic sequence datasets (that is, whole genome or whole exome) from newborns with known newborn screening results (positive or negative). Inclusion of diverse populations will be encouraged. A complementary SBIR/STTR program will also be initiated to provide support for relevant technology development.

All studies will conduct research demonstrating how genomic information compares with data obtained from current commonly-applied newborn screening. More specifically, each applicant will be expected to collect a comprehensive genomic dataset from infants with known newborn screening results and analyze those data in the context of one or more of the research questions below:

A. For disorders currently screened for in newborns, how can genomic sequencing replicate or augment (e.g., make more accurate, comprehensive or inexpensive) known newborn screening results?
B. What knowledge about conditions not currently screened for in newborns could genomic sequencing of newborns provide?
C. What additional clinical information could be learned from genomic sequencing relevant to the clinical care of newborns?

Each applicant must propose a research plan that includes the following three components: 1) large-scale data collection and analysis; 2) clinical research; and 3) ELSI research. The methods and scope of the research in all three of these areas should be tailored to the research context in which the sequencing is performed; for example, whether the focus is on previously diagnosed individuals and their families vs. a broader representation of newborns, or on currently screened for disorders vs. disorders not currently screened for.

Component 1 (Large-scale data collection and analysis) would involve acquisition and analysis of genomic datasets that expand considerably, in comparison with current routine data collection for newborns, the scale of data available in the newborn period. The types of genomic data (in addition to germline DNA sequence) that may be collected and analyzed include: epigenome (DNA methylation and/or histone modification), and transcriptome data. This might involve applying existing or developing new sequencing technologies to obtain high quality genomic sequence data from newborns, with or without epigenomic, and/or transcriptomic data, or comparing the quality of comprehensive sequence data obtained from dried blood spots to that from fresh blood.

Component 2 (Clinical Research) would involve studies that advance understanding of health and disease through genomic sequencing of newborns. This might involve correlating genomic information with phenotypic data to determine prognostic factors for disorders identified by newborn screening or identifying added clinical utility of newborn genomic data.

Component 3 (ELSI Research) would involve studies related to the societal (including ethical, psychosocial, legal, and economic) issues that may arise from the possible

implementation of genomic sequencing of newborns. This might involve examining whether and how to return genomic sequence results to patients, parents, or clinicians or identifying and addressing the issues and challenges related to informed consent.

Applicants are expected to describe for what sorts of research use and/or data sharing study participants have given or will be asked to give informed consent. All samples collected must have consent specifically for genomic sequencing research, and, if appropriate, the possible return of research results. Applicants will be expected to describe their proposed consent process explicitly. Funding may be requested for newborn sample collection, re-sampling, and/or re-consent for sequencing and data sharing. Applicants not proposing to conduct whole exome or whole genome sequencing will not be considered responsive. Deposition of individual level data in dbGaP will be expected in keeping with NHGRI and NIH policies.

Applicants will be expected to describe the process they will use to determine which specific categories of individual sequence results will or will not be offered to patients, parents, and/or clinicians, the reasoning behind decisions to return or not return results, and, if applicable how the results will be returned. Applicants may also be invited to propose serving as an Administrative Coordinating Center to provide administrative and logistical support. High programmatic priority will be given to studies that include multiple diseases or traits, return of results, ethnically diverse populations, larger sample sizes sufficient to demonstrate clinical relevance, children studied within five years of newborn screening, and are appropriate for broad data sharing and general research purposes.

Shortly after award, investigators will meet to share proposed study designs, sequencing methods, clinical phenotyping strategies, and quality control approaches and to identify potential common analyses and ELSI research that might be undertaken. They will meet again regularly to report on progress, identify common goals and best practices, and discuss lessons learned. This program will also coordinate with related programs such as the complementary SBIR/STTR program “Development of Genomic Technologies for Non-invasive Sample Collection Methods”, and the Return of Results and Large-Scale Sequencing programs at NHGRI.

Mechanism of Support

This initiative would use the NIH U19 (Cooperative Agreement) award mechanism. Up to five U19 awards would be made.

Funds Available

NHGRI and NICHD will each commit roughly $2.5M per year for five years ($25M total for both ICs) to support these awards. The five-year duration is needed to allow for longitudinal follow-up of newborns to assess impact on clinical care. Several other ICs have expressed interest in participating depending on the diseases/disorders proposed by applicants.