Concept Clearance for RFA (U19)

High Throughput Genomic Analysis in Children with Newborn Screening Disorders

National Advisory Council for Human Genome Research, February 2012

Purpose

The National Human Genome Research Institute (NHGRI) and Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) propose an RFA to explore opportunities to use genomic sequence information to broaden our understanding of diseases relevant to 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 the analysis of medical risks relevant to 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 broad DNA-based screening 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 saved 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 (table at the end of this document) 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 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 to conduct 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 4-5 pilot studies to collect comprehensive genomic sequence datasets (that is, whole genome, whole exome, or targeted sequencing of at least 500 relevant genes) from affected newborns and analyze those data in the context of diagnosis or treatment of a medical condition relevant to the newborn period. Inclusion of diverse populations will also be encouraged, including but not limited to minority and health disparity populations. A complementary SBIR/STTR program will also be initiated to provide support for technology development relevant to clinical and research settings that benefit from facile, non-invasive sample collection and cost-effective sample storage at very large scale.

All studies will conduct research demonstrating how genomic information complements data obtained from current commonly-applied newborn screening tests in 3 coordinated areas applicable to newborn screening: 1) large-scale data collection and analysis; 2) clinical research; and 3) ELSI research. More specifically, each applicant will be expected to collect a comprehensive genomic dataset from infants with a confirmed positive newborn screen (for any condition currently screened for by a state newborn screening program) and analyze those data in the context of a scientific question relevant to the diagnosis or treatment of a medical condition relevant to the newborn period. Focusing on confirmed positive infants will target the newborn population most likely to receive benefit from genomic sequencing with regard to clinical care, as well as permit evaluation of sequencing methods in a smaller sample size. 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. Each application will also be expected to propose research that examines the ethical, legal, and social implications of the generation and use of genomic sequence information from newborns.

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 for the analysis of medical risks relevant to the newborn period. 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 specific disorders identified via newborn screening through promising new DNA-based analysis. This might involve correlating genomic information with phenotypic data to determine prognostic factors for disorders identified through newborn screening or identifying added clinical utility of newborn genomic data compared to newborn screening results.

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 broad DNA-based screening of newborns. This might involve examining how return of DNA-based newborn screening results may affect the health behaviors and psychosocial well-being

of both parents and children or identifying and addressing the ethical, legal and social issues and challenges related to informed consent for this type of screening.

Applicants will be expected to present a plan for return of sequencing results including a detailed description of the process to determine which specific categories of individual sequence results will or will not be offered to patients and clinicians, how the results will be returned to the patient and clinician and incorporated into the medical record, and how any necessary follow-up (e.g., genetic counseling, referrals for additional testing) will be handled. Funding may be requested for newborn sample collection and/or re-consent for sequencing. Applicants proposing to study a single or a few genes/products will not be considered responsive. Highest priority will be given to studies covering a larger proportion of the genome. Deposition of individual level data in dbGaP will be expected in keeping with NHGRI and NIH policies if the data used have not already been deposited. 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 address multiple diseases or traits, return of results, ethnically diverse populations, larger sample sizes sufficient to demonstrate clinical relevance, no data use limitations, and children studied within 5 years of newborn screening.

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

Mechanism of Support

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

Funds Available

NHGRI and NICHD will each commit roughly $2.5M per year for 5 years ($25M total for both ICs) to support these awards. The 5-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/conditions proposed by applicants.

SACHDNC Recommended Uniform Screening Panel[1] Core[2] Conditions[3]

(as of January 2012)

Core Condition	Condition Type	Incidence[1]
Propionic academia	Organic acid	>1 in 75,000
Methylmalonic acidemia (methylmalonyl-CoA mutase)	Organic acid	>1 in 75,000
Methylmalonic acidemia (cobalamin disorders)	Organic acid	<1 in 100,000
Isovaleric acidemia	Organic acid	<1 in 100,000
3-Methylcrotonyl-CoA carboxylase deficiency	Organic acid	>1 in 75,000
3-Hydroxy-3-methyglutaric aciduria	Organic acid	<1 in 100,000
Holocarboxylase synthase deficiency	Organic acid	<1 in 100,000
ß-Ketothiolase deficiency	Organic acid	<1 in 100,000
Glutaric acidemia type I	Organic acid	>1 in 75,000
Carnitine uptake defect/carnitine transport defect	Fatty acid oxidation	<1 in 100,000
Medium-chain acyl-CoA dehydrogenase deficiency	Fatty acid oxidation	>1 in 25,000
Very long-chain acyl-CoA dehydrogenase deficiency	Fatty acid oxidation	>1 in 75,000
Long-chain L-3 hydroxyacyl-CoA dehydrogenase deficiency	Fatty acid oxidation	>1 in 75,000
Trifunctional protein deficiency	Fatty acid oxidation	<1 in 100,000
Argininosuccinic aciduria	Amino acid	<1 in 100,000
Citrullinemia, type I	Amino acid	<1 in 100,000
Maple syrup urine disease	Amino acid	<1 in 100,000
Homocystinuria	Amino acid	<1 in 100,000
Classic phenylketonuria	Amino acid	>1 in 25,000
Tyrosinemia, type I	Amino acid	<1 in 100,000
Primary congenital hypothyroidism	Endocrine	>1 in 5,000
Congenital adrenal hyperplasia	Endocrine	>1 in 25,000
S,S disease (Sickle cell anemia)	Hemoglobin	>1 in 5,000
S, βeta-thalassemia	Hemoglobin	>1 in 50,000
S,C disease	Hemoglobin	>1 in 25,000
Biotinidase deficiency	Other	>1 in 75,000
Cystic fibrosis	Other	>1 in 5,000
Classic galactosemia	Other	>1 in 50,000
Hearing loss	Other	>1 in 5,000
Severe Combined Immunodeficiences	Other	>1 in 75,000
Critical Congenital Cyanotic Heart Disease	Other	>1 in 5,000

1. The selection of these conditions is based on the report “Newborn Screening: Towards a Uniform Screening Panel and System. Genet Med. 2006; 8(5) Suppl: S12-S252” as authored by the American College of Medical Genetics (ACMG) and commissioned by the Health Resources and Services Administration (HRSA). Incidences listed are also from this report.
2. Disorders that should be included in every Newborn Screening Program
3. The Nomenclature for Conditions is based on the report “Naming and Counting Disorders (Conditions) Included in Newborn Screening Panels” Pediatrics 2006; 117 (5) Suppl: S308-S314

Table modified from:
http://www.hrsa.gov/advisorycommittees/mchbadvisory/heritabledisorders/recommendedpanel/