Department of Health and Human Services

Part 1. Overview Information

Participating Organization(s)	National Institutes of Health (NIH)
Components of Participating Organizations	*Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) National Human Genome Research Institute (NHGRI)
Funding Opportunity Title	**Genomic Sequencing and Newborn Screening Disorders (U19)**
Activity Code	U19 Research Program – Cooperative Agreements
Announcement Type	New
Related Notices	None
Funding Opportunity Announcement (FOA) Number	**RFA-HD-13-010**
Companion Funding Opportunity	None
Number of Applications	See Section III. 3. Additional Information on Eligibility.
Catalog of Federal Domestic Assistance (CFDA) Number(s)	93.865
Funding Opportunity Purpose	The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) and The National Human Genome Research Institute (NHGRI) invite applications that propose to explore the implications, challenges and opportunities associated with the possible use of genomic sequence information in the newborn period. Funds will be used to stimulate research in three component projects specifically applicable to newborn screening: • Acquisition and analysis of genomic datasets that expand considerably the scale of data available for analysis in the newborn period; • Clinical research that will advance understanding of specific disorders identifiable via newborn screening through promising new DNA-based analysis; and • Research related to the ethical, legal and social implications

	(ELSI) of the possible implementation of genomic sequencing of newborns. Each research project will be expected to collect a comprehensive genomic dataset from infants with known newborn screening results (positive or negative) and analyze those data in the context of one or more of the following research questions: • For disorders currently screened for in newborns, how can genomic sequencing replicate or augment known newborn screening results? • What knowledge about conditions not currently screened for in newborns could genomic sequencing of newborns provide? • What additional clinical information could be learned from genomic sequencing relevant to the clincial care of newborns? Applicants must include coordinated research in each of the three Component Projects and address one or more of the research questions listed to be considered responsive to the FOA.

Key Dates

Posted Date	August 9, 2012
Letter of Intent Due Date	October 19, 2012
Application Due Date(s)	November 19, 2012
AIDS Application Due Date(s)	Not Applicable.
Scientific Merit Review	February/March 2013
Advisory Council Review	May 2013
Earliest Start Date(s)	July 1, 2013
Expiration Date	November 20, 2012
Due Dates for E.O. 12372	Not Applicable.

Required Application Instructions

It is critical that applicants follow the instructions in the PHS398 Application Guide except where

instructed to do otherwise (in this FOA or in a Notice from the *NIH Guide for Grants and Contracts*). Conformance to all requirements (both in the Application Guide and the FOA) is required and strictly enforced. While some links are provided, applicants must read and follow all application instructions in the Application Guide as well as any program-specific instructions noted in Section IV. When the program-specific instructions deviate from those in the Application Guide, follow the program-specific instructions. **Applications that do not comply with these instructions may be delayed or not accepted for review.**

Note: A new version of the paper PHS 398 application form and instructions (revised 6/2009) must now be used. Download the new application form and instructions from http://grants.nih.gov/grants/forms.htm.

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Part 2. Full Text of Announcement

Section I. Funding Opportunity Description

Purpose

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) and The National Human Genome Research Institute (NHGRI) invite applications that propose to explore the implications, challenges and opportunities associated with the possible use of genomic sequence information in the newborn period. Funds will be used to stimulate research in three component projects specifically applicable to newborn screening:

- Acquisition and analysis of genomic datasets that expand considerably the scale of data available for analysis in the newborn period;
- Clinical research that will advance understanding of specific disorders identifiable via newborn screening through promising new DNA-based analysis; and
- Research related to the ethical, legal and social implications (ELSI) of the possible implementation of genomic sequencing of newborns.

Each research project will be expected to collect a comprehensive genomic dataset from infants with known newborn screening results (positive or negative) and analyze those data in the context of one or more of the following research questions:

- For disorders currently screened for in newborns, how can genomic sequencing replicate or augment known newborn screening results?
- What knowledge about conditions not currently screened for in newborns could genomic sequencing of newborns provide?
- What additional clinical information could be learned from genomic sequencing relevant to the clincial care of newborns?

Applicants must include coordinated research in each of the three component projects and address one or more of the research questions listed to be considered responsive to the FOA.

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 gene products or DNA) performed in the United States. This public health program has saved countless lives through the identification of infants who are at risk for congenital disorders for which early interventions and treatments have the potential to reduce morbidity and mortality. States routinely screen newborns for at least 30 congenital disorders.

The role and scope of newborn screening in the United States has continually evolved since its inception in the 1960's. For example, the availability of new technologies such as tandem mass spectrometry has dramatically increased the number of screenable disorders, and also has allowed identification of so-called secondary targets that are typically part of the differential diagnosis for core disorders.

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 comprehensive 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 in the future and substantially expand its clinical and public health value. Recognizing these trends, NICHD, NHGRI and ORDR held a workshop in December 2010 to identify elements of a trans-NIH research agenda that could inform the possible application of new genomic concepts and technologies to newborn screening and child health. (http://www.nichd.nih.gov/about/meetings/2010/121410.cfm). This FOA represents an initial step along this path. The purpose of this initiative is to explore, in a limited but deliberate manner, opportunities to use genomic information for broadening our understanding of diseases identified in the newborn period.

Specific Areas of Interest

In keeping with the spirit of the 2008 Newborn Screening Saves Lives Act (P.L. 110-204) that authorizes the NIH to carry out research in newborn screening, it is the intent of this initiative to encourage the exploration of specific scientific challenges and opportunities related to the use of emerging genomic technologies and concepts in the context of newborn screening. Interested NIH

institutes (including NICHD, NHGRI) intend to support studies to collect comprehensive genomic sequence datasets (that is, whole genome or whole exome) from newborns with known newborn screening results (positive or negative). All studies will conduct research demonstrating how genomic information compares with data obtained from current commonly-applied newborn screening.

In order to be considered responsive to the FOA, 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:

Question 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?

Question B) What knowledge about conditions not currently screened for in newborns could genomic sequencing of newborns provide?

Question C) What additional clinical information could be learned from genomic sequencing relevant to the clinical care of newborns?

In order to be considered responsive to the FOA, each applicant must also propose a research plan that includes each of the following three component projects:

Research Component 1) acquisition and analysis of genomic datasets that expand considerably the scale of data available for analysis in the newborn period;

Research Component 2) clinical research that will advance understanding of specific disorders identifiable via newborn screening through promising new DNA-based analysis; and

Research Component 3) research related to the ethical, legal and social implications (ELSI) of the possible implementation of genomic sequencing of newborns.

The methods and scope of the research in all three of these component projects should be tailored to focus on the newborn period and the research context in which the sequencing is performed.

Component Project 1

This FOA requires the collection and analysis, for each participant, of a “large genomic dataset” which, in this context means a collection of high-quality nucleic acid data from all or a large portion of the genome of each of the study participants. ***At a minimum*** the scale of data that is required is whole genome or whole exome. 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. Applications that propose to sequence individual genes or sets of genes, that only use microarray data, or that only assay a small number of elements (e.g., PCR products), will be considered non responsive.

Component Project 1 (Large-scale data collection and analysis) would involve acquisition and analysis of a large genomic dataset that expand considerably, in comparison with current routine data collection for newborns, the scale of data available in the newborn period.

Possible research topics may include, but are not limited to:

- Applying existing sequencing technologies with appropriate sensitivity, accuracy, high throughput, speed and low cost to obtain high-quality large genomic sequence dataset from newborns;
- Developing new sequencing technologies with appropriate sensitivity, accuracy, high throughput, speed and low cost to obtain high-quality large genomic sequence dataset from newborns;
- Comparing the quality of comprehensive sequence data obtained by using DNA isolated from dried blood spots, to that from fresh blood or other relevant samples of demonstrated quality.

Component Project 2

This component of the FOA focuses on disorders that are currently identified by NBS or that could potentially benefit from early identification by newborn screening.

Component Project 2 (Clinical Research) would involve studies that advance understanding of specific disorders identifiable via newborn screening through promising new DNA-based analysis

Possible research topics may include but are not limited to:

- Correlating genetic, genomic, and/or pharmacogenomic information with phenotypic data to determine prognostic factors in disease presentation, progression, and response to therapy for disorders identified through newborn screening;
- Identifying the relevance of genetic variants;
- Developing an analysis pipeline that improves quality and interpretation of newborn genomic data as a function of the availability of one or both parents' genomic information.

Component Project 3

This component of the FOA focuses on the ethical, legal and social implications of genetic and genomic research for individuals, families and communities.

Component Project 3 (ELSI Research) would involve studies related to the social (including ethical, psychosocial, legal, and economic) issues that may arise from the possible implementation of genomic sequencing of newborns.

Possible research topics may include but are not limited to:

- Examining how the possible return of DNA-based newborn screening results affects health behaviors and psychosocial well-being of both parents and children;
- Investigating decision-making frameworks (especially ethical and legal factors) for clinicians and other providers in deciding whether and how to return DNA-based results to individuals and their families;
- Exploring perspectives of parents and clinicians regarding their goals for and expectations about DNA-based newborn screening;
- Identifying and addressing the challenges related to informed consent for population-based newborn screening with potential lifelong implications, such as carrier status;
- Examining the issues regarding the ethical and legal status of the newborn undergoing DNA-based screening;
- Exploring the legal, economic, social and institutional challenges of the possible use of genomic screening technologies by existing newborn screening programs.

Section II. Award Information

Funding Instrument	Cooperative Agreement
Application Types Allowed	New The OER Glossary and the PHS398 Application Guide provide details on these application types.
Funds Available and Anticipated Number of Awards	NICHD and NHGRI intend to commit an estimated total of $25,000,000.
Award Budget	Application budgets should not exceed total costs of $1.25 million dollars per year, and must reflect actual needs of proposed research project.
Award Project Period	The scope of the proposed project should determine the project period. The maximum period is 5 years.

NIH grants policies as described in the *NIH Grants Policy Statement* will apply to the applications submitted and awards made in response to this FOA.

Section III. Eligibility Information

1. Eligible Applicants

Eligible Organizations

Higher Education Institutions

- Public/State Controlled Institutions of Higher Education
- Private Institutions of Higher Education

The following types of Higher Education Institutions are always encouraged to apply for NIH support as Public or Private Institutions of Higher Education:

- Hispanic-serving Institutions
- Historically Black Colleges and Universities (HBCUs)
- Tribally Controlled Colleges and Universities (TCCUs)
- Alaska Native and Native Hawaiian Serving Institutions

Nonprofits Other Than Institutions of Higher Education

- Nonprofits with 501(c)(3) IRS Status (Other than Institutions of Higher Education)
- Nonprofits without 501(c)(3) IRS Status (Other than Institutions of Higher Education)

For-Profit Organizations

- Small Businesses
- For-Profit Organizations (Other than Small Businesses)

Governments

- State Governments
- County Governments
- City or Township Governments
- Special District Governments
- Indian/Native American Tribal Governments (Federally Recognized)
- Indian/Native American Tribal Governments (Other than Federally Recognized)
- Eligible Agencies of the Federal Government
- U.S. Territory or Possession

Other

- Independent School Districts
- Public Housing Authorities/Indian Housing Authorities
- Native American Tribal Organizations (other than Federally recognized tribal governments)
- Faith-based or Community-based Organizations
- Regional Organizations

Foreign Institutions

Non-domestic (non-U.S.) Entities (Foreign Institutions) **are not** eligible to apply.
Non-domestic (non-U.S.) components of U.S. Organizations **are not** eligible to apply.
Foreign components, as defined in the *NIH Grants Policy Statement*, **are not** allowed.

Required Registrations

Applicant organizations must complete the following registrations as described in the PHS398 Application Guide to be eligible to apply for or receive an award. Applicants must have a valid Dun and Bradstreet Universal Numbering System (DUNS) number in order to begin each of the following registrations.

- Central Contractor Registration (CCR) – must maintain an active registration, to be renewed at least annually
- eRA Commons

All Program Director(s)/Principal Investigator(s) (PD(s)/PI(s)) must also work with their institutional officials to register with the eRA Commons or ensure their existing eRA Commons account is affiliated with the eRA Commons account of the applicant organization.

All registrations must be completed by the application due date. Applicant organizations are strongly encouraged to start the registration process at least4-6 weeks prior to the application due date.

Eligible Individuals (Program Director(s)/Principal Investigator(s))

Any individual(s) with the skills, knowledge, and resources necessary to carry out the proposed research as the Program Director(s)/Principal Investigator(s) (PD(s)/PI(s)) is invited to work with his/her organization to develop an application for support. Individuals from underrepresented racial and ethnic groups as well as individuals with disabilities are always encouraged to apply for NIH support.

For institutions/organizations proposing multiple PD(s)/PI(s), visit the Multiple Program Director(s)/Principal Investigator(s) Policy and submission details in the Senior/Key Person Profile (Expanded) Component of the PHS398 Application Guide.

Expertise is essential in all areas addressed by the FOA: genomic analysis, newborn screening, clinical medicine, bioethics and social or behavioral sciences. One PD/PI should be designated as the lead for the grant. Designation of additional PD(s)/PI(s), with the appropriate experience and expertise to lead other components of the project, is encouraged, as suitable for the specific Research Plan.

The PD(s)/PI(s) must devote at least 1.8 person months effort to this Cooperative Agreement.

2. Cost Sharing

This FOA does not require cost sharing as defined in the *NIH Grants Policy Statement.*

3. Additional Information on Eligibility

Number of Applications

Applicant organizations may submit more than one application, provided that each application is scientifically distinct.

NIH will not accept any application in response to this FOA that is essentially the same as one currently pending initial peer review unless the applicant withdraws the pending application.

Section IV. Application and Submission Information

1. Address to Request Application Package

Applicants are required to prepare applications according to the current PHS 398 application forms in accordance with the PHS 398 Application Guide.

2. Content and Form of Application Submission

It is critical that applicants follow the instructions in the PHS398 Application Guide, except where instructed in this funding opportunity announcement to do otherwise. Conformance to the requirements in the Application Guide is required and strictly enforced. Applications that are out of compliance with these instructions may be delayed or not accepted for review.

Letter of Intent

Although a letter of intent is not required, is not binding, and does not enter into the review of a subsequent application, the information that it contains allows IC staff to estimate the potential review workload and plan the review.

By the date listed in Part 1. Overview Information, prospective applicants are asked to submit a letter of intent that includes the following information:

- Descriptive title of proposed research

- Name, address, and telephone number of the PD(s)/PI(s)
- Names of other key personnel
- Participating institutions
- Number and title of this funding opportunity

The letter of intent should be sent to:

Tiina K. Urv, Ph.D.
Intellectual and Developmental Disabilities Branch
Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)
6100 Executive Blvd.
Bethesda, MD 20892-7510
Rm 4B09D, MSC 7510
Phone: 301-402-7015
Email: urvtiin@mail.nih.gov

Application Submission

Applications must be prepared using the PHS 398 research grant application forms and instructions for preparing a research grant application. Submit a signed, typewritten original of the application, including the checklist, and three signed photocopies in one package to:

Center for Scientific Review
National Institutes of Health
6701 Rockledge Drive, Room 1040, MSC 7710
Bethesda, MD 20892-7710 (U.S. Postal Service Express or regular mail)
Bethesda, MD 20817 (for express/courier service; non-USPS service)

At the time of submission, two additional paper copies of the application and five identical copies of Appendix materials as CDs must be sent to:

Sherry Dupere, Ph.D.
Director, Division of Scientific Review
Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)
6100 Executive Boulevard, Room 5B01, MSC 7510
Bethesda, MD 20892-7510
Rockville, MD 20852 (for express/courier service; non-USPS service)
Telephone: 301-496-3415
Email: duperes@mail.nih.gov

Page Limitations

All page limitations described in the PHS398 Application Guide and the Table of Page Limits must be followed, with the following requirements:

- Overview of Project (Specific aims, 1 page; Overview, 6 pages)
- Component Project 1: Analysis and Assembly of Genomic Datasets (Research Strategy- 12 pages)
- Component Project 2: Clinical Research of Disorders Identifiable through Newborn Screening (Research Strategy - 12 pages)
- Component Project 3: Ethical and Social Implications of Research related to DNA-based

analysis associated with Newborn Screening (Research Strategy - 12 pages)

Face Page (Form Page 1)

Include the number and title of this FOA in item/line 2 of the PHS 398 face page

Table of Contents (Form Page 3)

Modify PHS398 Form Page 3 to enable reviewers to find each component of the application easily. Number all pages consecutively. Because the first page of the application is the Title Page begin the next page with the numeral "2". Do not use lettered numbers (e.g., "2A", "2B" etc.). Use these referent numbers in the Table of Contents.

Detailed Budget for Initial Budget Period

Budget for Entire Proposed Period of Support

Prepare a detailed composite budget (across all subprojects) for all requested support categories for the first year using Form Page 4 and a summary budget for the entire proposed period of support using Form Page 5 of the PHS 398 application. If applicable, provide additional budget pages for consortium/contractual arrangements.

PD(s)/PI(s) for the overall project and for each Component Project are required to devote at least 1.8 person-months of effort.

PD(s)/PI(s) and Component Project PD(s)/PI(s) are required to attend the following meetings, and should include travel funds in the budget accordingly:

- One in-person meeting involving research projects funded under this FOA and the External Scientific Panel.
- Two research project steering committee meetings (in-person or virtual).

Biographical Sketch

Investigators or key personnel who participate in more than one component of the project should describe and justify their different roles in the Personal Statement of the Biosketch.

Resources

Reviewers will use information from the Resources page to evaluate the quality of the scientific environment for the research proposed. Applicants should complete separate Resources pages for all projects.

Research Plan

All instructions in the PHS398 Application Guide must be followed, with the following additional instructions:

The Research Plan must include an Overview of the Project as well as sections devoted to each of the three required Component Projects.

Begin each section with a new PHS 398 Continuation Page. Do not use the PHS 398 Face Page. Include the PD(s)/PI(s) name at the upper right-hand corner of each page.

Overview of the Project

Specific Aims (1 page)

Describe the aims of the overall research project and outline how the component projects will contribute to these aims.

Overall Program Objectives (6 pages)

Items 1, 2 and 3 below are to be included in the six page limit.

1. Significance: Focusing on the research project as a whole address (i) the importance of the problem or critical barrier to progress in the field that the proposed research project addresses, (ii) how the proposed research project will improve scientific knowledge, technical capability, and/or clinical practice in one or more broad fields, (iii) how the concepts methods, technologies, treatments, services, or preventive interventions that drive this field will be changed if the proposed aims are achieved. (One to two pages recommended).

2. Innovation: Considering the research project as a whole, show how the proposed research seeks to shift current research or clinical practice paradigms through use of novel concepts, approaches, methodologies, instrumentation, or interventions. Are these concepts, approaches, methodologies, instrumentation, or interventions novel to the research field or novel in a broad sense? Does the proposed work refine, or improve, or apply in a new way, the concepts, approaches, methodologies, instrumentation, or interventions proposed?(One page recommended).

3. Approach: Include the major approaches and studies involved in the application showing how the approaches of individual component projects complement each other or are inter-dependent. Describe the mechanisms that will ensure the coherence of the overall research project and maintain a multidisciplinary focus. (Three to four pages recommended.)

Overall Program Objectives should also address the following:

- Identify which research question(s) is/are being addressed by the research project
- Question 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?
- Question B) What knowledge about conditions not currently screened for in newborns could genomic sequencing of newborns provide?
- Question C) What additional clinical information could be learned from genomic sequencing relevant to the clinical care of newborns?
- A detailed description of and interdependent associations between Component Projects 1, 2, and 3, including a description of how each component project will be integrated into the overall research project.
- A description of management structure, leadership roles, and mechanisms of communication;
- A detailed description of the informed consent or re-consent process, including consent for genomic sequencing, data sharing, and return of results.
- A description of institutional human subject's protections and oversight.

- Specific Aims for the overall research project and each component project.
- Potential relevance to newborn screening programs.

Applicants are strongly encouraged to leverage existing resources such as the NICHD-funded Newborn Screening Translational Research Network (NBSTRN) https://www.nbstrn.org and the NHGRI-funded Sequencing Centers http://www.genome.gov/10001691.

Component Project 1- Analysis and Assembly of Genomic Datasets

Specific Aims (1 page)

Research Strategy (12 pages)

Following the PHS 398 Instructions, the Research Strategy for Component Project 1 should be organized into sections on: a. Significance; b. Innovation; and c. Approach. In addition to those sections, the Research Strategy should include the following:

A) Genomic Sequencing Plan

- Description of specimen processing and tracking.
- Justification for and description of the genomic sequencing strategy description of the proposed study sample, including details on study design, sample size, selection, and plans for obtaining appropriate informed consent or re-consent of individuals for genomic sequencing and data deposition.
- Description of genomic sequence generation, the facilities and instrumentation to be utilized for sequence generation or, if sequencing is to be subcontracted, the sequence provider.
- Detailed description of genomic sequencing experience and demonstration of quality data production at the scale required to achieve component project goals; it is suggested that a report on the prior quarter's sequencing production and quality measures employed be included.
- Detailed description of bioinformatics infrastructure/capabilities to securely transmit and store genomic data files for the research project.
- Description of the pipeline from acquisition of specimens through sequencing data generation, including time components.
- A clear statement of the scientific question(s) being addressed related to technology development for collecting a large genomic dataset in the newborn screening context, if applicable.

B) Genomic Sequence Analysis

- Description of computational and analysis resources
- Description of anticipated analysis strategy, including file hierarchy and structure, and primary sequence data quality assessments
- Description of variation calling strategy, including algorithm development, if any
- Preliminary results

C) Costs

- An itemized breakdown of costs per patient for genomic sequencing and primary analysis

Component Project 2 - Clinical Research of Disorders Identifiable

through Newborn Screening

Specific Aims (1 page)

Research Strategy (12 pages)

Following the PHS 398 Instructions, the Research Strategy for Component Project 2 should be organized into sections on: a. Significance; b. Innovation; and c. Approach. In addition to those sections, the Research Strategy should include the following:

A) Clinical Interpretation and Transmission of Results

- A clear statement of the research question(s) being addressed by use of a large genomic dataset, and how that information will enhance understanding of a disorder identifiable via newborn screening, particularly with regard to disease presentation, progression, and/or response to therapy (pharmacogenomics).
- For individuals with a confirmed positive NBS disorder, a specific plan for coordination with State Newborn Screening Programs, if appropriate to the research question.
- A detailed description of the analysis tools and the methodologies to address the research questions posed, including an algorithm to determine whether genetic or genomic variants are relevant or clinically actionable and integration of parental genomic information, if appropriate.
- A detailed description of the clinical approach to phenotypic assessment, evaluation, and follow-up for individuals with a condition identifiable in the newborn period.
- Applicants are required to present a plan for return of results describing which results would be returned and the procedures for doing so. If no results are returned, a detailed rationale must be provided.
- Clear description of the expertise available to carry out research related to clinical and phenotypic evaluation, as well as experience related to state newborn screening programs, their principles, practices and policies.
- A description of anticipated challenges in the analysis plan, and strategies to overcome these challenges.

B) Cost

- An estimate of cost per patient for clinical evaluation, phenotypic evaluation, and return of results.

Component Project 3 - Ethical and Social Implications of Research Related to DNA-based Analysis Associated with Newborn Screening

Specific Aims (1 page)

Research Strategy (12 pages)

Following the PHS 398 Instructions, the Research Strategy for Component Project 3 should be organized into sections on: a. Significance; b. Innovation; and c. Approach. In addition to those sections, the Research Strategy should include the following:

- A clear statement of the specific research questions being addressed, and how addressing these questions will enhance understanding of the implications of the possible implementation of broad DNA-based screening of newborns.

- A detailed description of and rationale for the approaches and methodologies that will be used to study these questions.
- A concise description of how this component project will be integrated into the development and implementation of the overall study design, including the informed consent process and return of results.
- Clear description of the expertise available to design, lead and carry out the ELSI Research component project, and how this expertise will be utilized in the development and implementation of the overall study.

Protection of Human Subjects

List the components of the application that involve human subjects and page numbers for the relevant human subjects sections. Follow PHS 398 Instructions for describing appropriate human subjects protections. These descriptions may be included under each Component Project or in one composite section of the application.

Inclusion of Women, Minorities and Children

Describe the composition of the human subjects and the proactive plan to recruit women, minorities, and children (if appropriate). List the page numbers for the relevant Women, Minorities, and Children sections. Follow PHS 398 Instructions in preparing this section. These descriptions may be included under each Component Project or in one composite section of the application.

Resource Sharing Plan

Individuals are required to comply with the instructions for the Resource Sharing Plans (Data Sharing Plan, Sharing Model Organisms, and Genome Wide Association Studies (GWAS)) as provided in the PHS398 Application Guide, with the following modifications:

- The NHGRI large-scale sequencing program has long championed the concept of rapid pre-publication data release. However, privacy issues associated with clinical research, such as in the program described in this FOA, can provide a rationale for exception to those long-held precepts. Some genomic sequencing and variation data sets generated as a result of this research may become a part of an individual patient's medical record. However, sequence and phenotype data resulting from this research may have value beyond that intended by the submitting investigators. Therefore, submission of study data sets to the database of Genotype and Phenotype (dbGaP), while not required before publication, is encouraged, and should be released at the time of publication, within the rules and regulations of the controlling IRB and local jurisdiction and with informed consent to permit broad data release via an NIH database. Applications to this FOA are expected to include a discussion of how release to dbGaP will be authorized in the informed consent for the study, consistent with achieving the goals of the program. Any restrictions on data use (such as limitations to a specific disease or condition) should be described. Although this information is expected to be included in the application, the plans for data sharing will not be factored into the Overall Impact score.
- The general NIH data sharing policy is available at http://grants.nih.gov/grants/policy/data_sharing. All investigators responding to this funding opportunity and requesting $500,000 or more per year in direct costs are expected to include a description of how research data will be shared.

Appendix

Do not use the Appendix to circumvent page limits. Follow all instructions for the Appendix (please note all format requirements) as described in the PHS398 Application Guide.

3. Submission Dates and Times

Part I. Overview Information contains information about Key Dates.

Information on the process of receipt and determining if your application is considered “on-time” is described in detail in the PHS398 Application Guide.

Applicants may track the status of the application in the eRA Commons, NIH’s electronic system for grants administration.

4. Intergovernmental Review (E.O. 12372)

This initiative is not subject to intergovernmental review.

5. Funding Restrictions

All NIH awards are subject to the terms and conditions, cost principles, and other considerations described in the *NIH Grants Policy Statement*.

Pre-award costs are allowable only as described in the *NIH Grants Policy Statement*.

6. Other Submission Requirements and Information

Applications must be postmarked on or before the due dates in Part I. Overview Information.

Upon receipt, applications will be evaluated for completeness by the Center for Scientific Review and responsiveness by componants of participating organizations, NIH. Applications that are incomplete and/or nonresponsive will not be reviewed.

In order to be considered responsive to the FOA each application must include three highly integrated Component Projects that include each of the following:

Component Project 1: Acquisition and analysis of genomic datasets that expand considerably the scale of data available for analysis in the newborn period

Component Project 2: Clinical research that will advance understanding of specific disorders identifiable via newborn screening through promising new DNA-based analysis

Component Project 3: Research related to the ethical, legal and social implications (ELSI) of the possible implementation of genomic sequencing of newborns

Each research project must also address one or more of the following questions:

Question 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?

Question B) What knowledge about conditions not currently screened for in newborns could genomic sequencing of newborns provide?

Question C) What additional clinical information could be learned from genomic sequencing relevant to the clinical care of newborns?

Pre-Application Information Call and On-Line Information

The NIH will hold a pre-application informational conference call on August 29, 2012, at 2:00 pm – 3:30 pm EST, to which all interested prospective applicants are invited. Program and review staff will make presentations to explain the goals and objectives of the FOA and will answer questions from call participants.

To obtain, the call-in information, please contact Dr. Tiina Urv (urvtiin@mail.nih.gov) at least 24 hours prior to the call.

Post Submission Materials

Applicants are required to follow the instructions for post-submission materials, as described in NOT-OD-10-115.

Section V. Application Review Information

1. Criteria

Only the review criteria described below will be considered in the review process. As part of the NIH mission, all applications submitted to the NIH in support of biomedical and behavioral research are evaluated for scientific and technical merit through the NIH peer review system.

Overall Impact

Reviewers will provide an overall impact/priority score to reflect their assessment of the likelihood for the project to exert a sustained, powerful influence on the research field(s) involved, in consideration of the following review criteria and additional review criteria (as applicable for the project proposed).

Scored Review Criteria - Overall

Reviewers will consider each of the review criteria below in the determination of scientific merit, and give a separate score for each. An application does not need to be strong in all categories to be judged likely to have major scientific impact. For example, a project that by its nature is not innovative may be essential to advance a field.

Significance

Does the project address an important problem or a critical barrier to progress in the field? If the aims of the project are achieved, how will scientific knowledge, technical capability, and/or clinical practice be improved? How will successful completion of the aims change the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field?

Investigator(s)

Are the PD(s)/PI(s), collaborators, and other researchers well suited to the project? If Early Stage Investigators or New Investigators, or in the early stages of independent careers, do they have appropriate experience and training? If established, have they demonstrated an ongoing record of accomplishments that have advanced their field(s)? If the project is collaborative or multi-PD(s)/PI(s), do the investigators have complementary and integrated expertise; are their leadership approach, governance and organizational structure appropriate for the project?

Innovation

Does the application challenge and seek to shift current research or clinical practice paradigms by utilizing novel theoretical concepts, approaches or methodologies, instrumentation, or interventions? Are the concepts, approaches or methodologies, instrumentation, or interventions novel to one field of research or novel in a broad sense? Is a refinement, improvement, or new application of theoretical concepts, approaches or methodologies, instrumentation, or interventions proposed?

Approach

Are the overall strategy, methodology, and analyses well-reasoned and appropriate to accomplish the specific aims of the project? Are potential problems, alternative strategies, and benchmarks for success presented? If the project is in the early stages of development, will the strategy establish feasibility and will particularly risky aspects be managed?

If the project involves clinical research, are the plans for 1) protection of human subjects from research risks, and 2) inclusion of minorities and members of both sexes/genders, as well as the inclusion of children, justified in terms of the scientific goals and research strategy proposed?

Environment

Will the scientific environment in which the work will be done contribute to the probability of success? Are the institutional support, equipment and other physical resources available to the investigators adequate for the project proposed? Will the project benefit from unique features of the scientific environment, subject populations, or collaborative arrangements?

Additional Review Criteria - Overall

As applicable for the project proposed, reviewers will evaluate the following additional items while determining scientific and technical merit, and in providing an overall impact/priority score, but will not give separate scores for these items.

Component Project 1 - Analysis and Assemby of Genomic Datasets

- Is the genomic sequencing strategy adequate?
- Does the proposed research team have adequate genome sequencing experience?
- Is the proposed research plan likely to yield high quality sequence data with reasonable turnaround time?
- Are the bioinformatics infrastructure/capabilities to securely transmit and store genomic data files for the research project adequate?

- Are the computational and analysis resources adequate?
- Is the analysis strategy appropriate for the proposed research?
- Are the costs per patient for genomic sequencing and primary analysis appropriate?
- Is the Analysis and Assembly of Genomic Datasets fully integrated with the other component projects of the research plan?

Component Project 2 - Clinical Research of Disorders Identifiable through Newborn Screening

- Is the analysis plan for identifying potentially clinically actionable variants, including a description of how sequence variants will be confirmed in a CLIA-certified laboratory adequate?
- Are the research question(s) being addressed by use of a large genomic dataset appropriate?
- Is the description of analysis tools and the methodologies to address the research questions adequate?
- Is the approach to phenotypic assessment appropriate and adequate for the application?
- Does the plan for return of results clearly describe which results will be returned and the procedure for doing so?
- If no results are to be returned, is a detailed rationale provided?
- Is the Clinical Research section full integrated with the other component projects of the research plan?

Component Project 3 - Ethical and Social Implications of Research Related to DNA-based Analysis Associated with Newborn Screening

- Are the ELSI research questions described clearly? Do they address highly relevant issues?
- Are the methodologies and approaches appropriate for the questions being addressed and are they described in sufficient detail?
- Is there a clear description of the expertise of the researchers who will design, lead and carry out the ELSI related research? Is this expertise appropriate?
- Is the Ethical and Social Implications research component project fully integrated with the other components of the research plan?

Overall

- Is the application equally strong across all three component projects?
- Do the projects collectively answer one or more of the questions?

Protections for Human Subjects

For research that involves human subjects but does not involve one of the six categories of research that are exempt under 45 CFR Part 46, the committee will evaluate the justification for involvement of human subjects and the proposed protections from research risk relating to their participation according to the following five review criteria: 1) risk to subjects, 2) adequacy of protection against risks, 3) potential benefits to the subjects and others, 4) importance of the knowledge to be gained, and 5) data and safety monitoring for clinical trials.

For research that involves human subjects and meets the criteria for one or more of the six categories of research that are exempt under 45 CFR Part 46, the committee will evaluate: 1) the justification for the exemption, 2) human subjects involvement and characteristics, and 3)

sources of materials. For additional information on review of the Human Subjects section, please refer to the Human Subjects Protection and Inclusion Guidelines.

Inclusion of Women, Minorities, and Children

When the proposed project involves clinical research, the committee will evaluate the proposed plans for inclusion of minorities and members of both genders, as well as the inclusion of children. For additional information on review of the Inclusion section, please refer to the Human Subjects Protection and Inclusion Guidelines.

Vertebrate Animals

The committee will evaluate the involvement of live vertebrate animals as part of the scientific assessment according to the following five points: 1) proposed use of the animals, and species, strains, ages, sex, and numbers to be used; 2) justifications for the use of animals and for the appropriateness of the species and numbers proposed; 3) adequacy of veterinary care; 4) procedures for limiting discomfort, distress, pain and injury to that which is unavoidable in the conduct of scientifically sound research including the use of analgesic, anesthetic, and tranquilizing drugs and/or comfortable restraining devices; and 5) methods of euthanasia and reason for selection if not consistent with the AVMA Guidelines on Euthanasia. For additional information on review of the Vertebrate Animals section, please refer to the Worksheet for Review of the Vertebrate Animal Section.

Biohazards

Reviewers will assess whether materials or procedures proposed are potentially hazardous to research personnel and/or the environment, and if needed, determine whether adequate protection is proposed.

Resubmissions

Not Applicable.

Renewals

Not Applicable.

Revisions

Not Applicable.

Additional Review Considerations - Overall

As applicable for the project proposed, reviewers will consider each of the following items, but will not give scores for these items, and should not consider them in providing an overall impact/priority score.

Applications from Foreign Organizations

Not Applicable.

Select Agent Research

Reviewers will assess the information provided in this section of the application, including 1) the Select Agent(s) to be used in the proposed research, 2) the registration status of all entities where Select Agent(s) will be used, 3) the procedures that will be used to monitor possession use and transfer of Select Agent(s), and 4) plans for appropriate biosafety, biocontainment, and security of the Select Agent(s).

Resource Sharing Plans

Reviewers will comment on whether the following Resource Sharing Plans, or the rationale for not sharing the following types of resources, are reasonable: 1) Data Sharing Plan; 2) Sharing Model Organisms; and 3) Genome Wide Association Studies (GWAS).

Budget and Period of Support

Reviewers will consider whether the budget and the requested period of support are fully justified and reasonable in relation to the proposed research.

2. Review and Selection Process

Applications will be evaluated for scientific and technical merit by (an) appropriate Scientific Review Group(s) convened by NICHD, in accordance with NIH peer review policy and procedures, using the stated review criteria. Review assignments will be shown in the eRA Commons.

As part of the scientific peer review, all applications:

- May undergo a selection process in which only those applications deemed to have the highest scientific and technical merit (generally the top half of applications under review) will be discussed and assigned an overall impact/priority score.
- Will receive a written critique.

Appeals of initial peer review will not be accepted for applications submitted in response to this FOA.

Applications will be assigned on the basis of established PHS referral guidelines to the appropriate NIH Institute or Center and will compete for available funds with all other recommended applications . Following initial peer review, recommended applications will receive a second level of review by the appropriate National Advisory Council or Board. The following will be considered in making funding decisions:

- Scientific and technical merit of the proposed project as determined by scientific peer review.
- Availability of funds.
- Relevance of the proposed project to program priorities. Programmatic priority will be given to studies that address multiple diseases or traits, return of results, ethnically diverse populations, sample sizes sufficient to demonstrate clinical relevance, children studied within 5 years of newborn screening.
- Applications that include samples that are appropriate for broad data sharing and general research purposes.

3. Anticipated Announcement and Award Dates

After the peer review of the application is completed, the PD(s)/PI(s) will be able to access his or her Summary Statement (written critique) via the eRA Commons.

Information regarding the disposition of applications is available in the *NIH Grants Policy Statement*.

Section VI. Award Administration Information

1. Award Notices

If the application is under consideration for funding, NIH will request "just-in-time" information from the applicant as described in the *NIH Grants Policy Statement*.

A formal notification in the form of a Notice of Award (NoA) will be provided to the applicant organization for successful applications. The NoA signed by the grants management officer is the authorizing document and will be sent via email to the grantee's business official.

Awardees must comply with any funding restrictions described in Section IV.5. Funding Restrictions. Selection of an application for award is not an authorization to begin performance. Any costs incurred before receipt of the NoA are at the recipient's risk. These costs may be reimbursed only to the extent considered allowable pre-award costs.

Any application awarded in response to this FOA will be subject to the DUNS, CCR Registration, and Transparency Act requirements as noted on the Award Conditions and Information for NIH Grants website.

2. Administrative and National Policy Requirements

All NIH grant and cooperative agreement awards include the *NIH Grants Policy Statement* as part of the NoA. For these terms of award, see the NIH Grants Policy Statement Part II: Terms and Conditions of NIH Grant Awards, Subpart A: General and Part II: Terms and Conditions of NIH Grant Awards, Subpart B: Terms and Conditions for Specific Types of Grants, Grantees, and Activities. More information is provided at Award Conditions and Information for NIH Grants.

Cooperative Agreement Terms and Conditions of Award

The following special terms of award are in addition to, and not in lieu of, otherwise applicable U.S. Office of Management and Budget (OMB) administrative guidelines, U.S. Department of Health and Human Services (DHHS) grant administration regulations at 45 CFR Parts 74 and 92 (Part 92 is applicable when State and local Governments are eligible to apply), and other HHS, PHS, and NIH grant administration policies.

The administrative and funding instrument used for this program will be the cooperative agreement, an "assistance" mechanism (rather than an "acquisition" mechanism), in which substantial NIH programmatic involvement with the awardees is anticipated during the performance of the activities. Under the cooperative agreement, the NIH purpose is to support and stimulate the recipients' activities by involvement in and otherwise working jointly with the award recipients in a partnership role; it is not to assume direction, prime responsibility, or a dominant role in the activities. Consistent with this concept, the dominant role and prime responsibility resides with the awardees for the project as a whole, although specific tasks and activities may be shared among the

awardees and the NIH as defined below.

The PD(s)/PI(s) will have the primary responsibility for:

The PD(s)/PI(s) will have primary authority and responsibility to define objectives and approaches and to plan and conduct the proposed research. She/he will assume responsibility and accountability to the applicant organization and to the NICHD and NHGRI for performance and proper conduct of all research, including the NIH intramural component, if applicable, in accordance with the Terms and Conditions of Award. The PD(s)/PI(s) will be a member of the Steering Committee (see below).

Intramural research scientists participating as collaborators have the same rights and responsibilities as other members of the Group (see below for Participation of NIH Intramural Scientists).

The Awardee Institution and/or Research Project Leader's Institution will retain primary custody of and have primary rights to data as specified under the data and research resource sharing plans (described above). The Government, via the NICHD and NHGRI Project Scientist(s), will have access to data generated under this cooperative agreement and may periodically review the data consistent with current DHHS, PHS, and NIH policies. Timely publication of major findings by the Group members is encouraged. Publication or oral presentation of work done under this agreement will require appropriate acknowledgment of NIH (NICHD and NHGRI) support, including the assigned cooperative agreement award number.

NIH staff have substantial programmatic involvement that is above and beyond the normal stewardship role in awards, as described below:

The Project Scientist(s) interacts scientifically with the Group and may provide appropriate assistance, including assisting in research planning, suggesting studies within the scope of the Group's objectives and research activities, presenting experimental findings to the Group from published sources or from relevant projects, participating in the design of experiments agreed to by the Group, participating in the analysis of results, and advising in management and technical performance. The Project Scientist(s) will be a member(s) of the Steering Committee. However, the total membership by NIH staff will not exceed one-third (1/3) of the membership of the Steering Committee. In all cases, the role of NICHD and NHGRI will be to assist and facilitate and not to direct activities.

Additionally, an NICHD and/or NHGRI Program Official will be responsible for the normal scientific and programmatic stewardship of the award, including monitoring implementation of the data and research resource sharing plans and will be named in the award notice.

Areas of Joint Responsibility include:

Steering Committee

Within two months of award, a Steering Committee will be established and chaired by the PD/PI. The Steering Committee will consist of the designated leaders for each Project, the NIH Project Scientist, other NIH scientists as identified by the PD(s)/PI(s) and/or Steering Committee, and any other key personnel identified by the PD(s)/PI(s). The NIH Project Scientist(s) will have one NIH vote. The Steering Committee may add additional members by majority vote.

Each full member will have one vote. Awardee members of the Steering Committee will be required

to accept and implement policies approved by the Steering Committee.

The Steering Committee will:

- Assist the PD(s)/PI(s) in achieving the goals.
- Evaluate progress of the Project and make recommendations for achieving Project goals.
- Be responsible for identifying policies and procedures to be implemented by the PD(s)/PI(s) to support operations and scientific progress, including development of guidelines for publication of the results of collaborative projects.
- Assist the PD(s)/PI(s), as required, in preparing formal reports summarizing activities and/or progress, such as the Annual Progress Report.
- Advise the NIH Project Scientist on scientific opportunities, emerging needs and impediments.
- Participate in monthly conference calls.
- Participate in in person/virtual meetings two times a year.
- Participate in one annual in person meeting involving all research projects funded under this FOA and the External Scientific Panel (meeting may coincide with individual Steering committee meetings).

The NIH Project Scientist will participate in the activities of the Steering Committee as required, providing verbal or written responses to the Steering Committee or its designated subcommittees upon request.

External Scientific Panel

An External Scientific Panel (ESP) composed of NICHD/NHGRI-appointed non-federal scientists, not affiliated with the awarded programs, will be established. This Panel is advisory to NICHD/NHGRI and will help assess progress, evaluate whether goals are being met, identify strengths and weaknesses, and make recommendations to NICHD/NHGRI regarding the program's success.

The ESP will meet at least once per year; a portion of which will be held jointly with a Steering Committee meeting.

Dispute Resolution:

Any disagreements that may arise in scientific or programmatic matters (within the scope of the award) between award recipients and the NIH may be brought to Dispute Resolution. A Dispute Resolution Panel composed of three members will be convened. It will have three members: a designee of the Steering Committee chosen without NIH staff voting, one NIH designee, and a third designee with expertise in the relevant area who is chosen by the other two; in the case of individual disagreement, the first member may be chosen by the individual awardee. This special dispute resolution procedure does not alter the awardee's right to appeal an adverse action that is otherwise appealable in accordance with PHS regulation 42 CFR Part 50, Subpart D and DHHS regulation 45 CFR Part 16.

3. Reporting

When multiple years are involved, awardees will be required to submit the Non-Competing Continuation Grant Progress Report (PHS 2590) annually and financial statements as required in the *NIH Grants Policy Statement.*

A final progress report, invention statement, and the expenditure data portion of the Federal Financial Report are required for closeout of an award, as described in the *NIH Grants Policy Statement*.

The Federal Funding Accountability and Transparency Act of 2006 (Transparency Act), includes a requirement for awardees of Federal grants to report information about first-tier subawards and executive compensation under Federal assistance awards issued in FY2011 or later. All awardees of applicable NIH grants and cooperative agreements are required to report to the Federal Subaward Reporting System (FSRS) available at www.fsrs.gov on all subawards over $25,000. See the *NIH Grants Policy Statement* for additional information on this reporting requirement.

Section VII. Agency Contacts

We encourage inquiries concerning this funding opportunity and welcome the opportunity to answer questions from potential applicants.

Application Submission Contacts

GrantsInfo (Questions regarding application instructions and process, finding NIH grant resources)
Telephone 301-435-0714
TTY 301-451-5936
Email: GrantsInfo@nih.gov

eRA Commons Help Desk (Questions regarding eRA Commons registration, tracking application status, post submission issues)
Phone: 301-402-7469 or 866-504-9552 (Toll Free)
TTY: 301-451-5939
Email: commons@od.nih.gov

Scientific/Research Contact(s)

Tiina K. Urv, Ph.D.
Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)
Telephone 301.402.7015
Email: urvtiin@mail.nih.gov

Anastasia L. Wise, Ph.D.
National Human Genome Research Institute (NHGRI)
Telephone: 301-443-0585
Email: anastasia.wise@nih.gov

Peer Review Contact(s)

Sherry Dupere, Ph.D.
Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)
Telephone: 301-496-3415
Email: duperes@mail.nih.gov

Financial/Grants Management Contact(s)

Bryan Clark, MBA

Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)
Telephone: 301-435-6975
Email: clarkb1@mail.nih.gov

Cheryl Chick
National Human Genome Research Institute (NHGRI)
Telephone: 301-402-0733
Email: cc149o@nih.gov

Section VIII. Other Information

Recently issued trans-NIH policy notices may affect your application submission. A full list of policy notices published by NIH is provided in the *NIH Guide for Grants and Contracts*. All awards are subject to the terms and conditions, cost principles, and other considerations described in the *NIH Grants Policy Statement*.

Authority and Regulations

Awards are made under the authorization of Sections 301 and 405 of the Public Health Service Act as amended (42 USC 241 and 284) and under Federal Regulations 42 CFR Part 52 and 45 CFR Parts 74 and 92.

Weekly TOC for this Announcement
NIH Funding Opportunities and Notices

Note: For help accessing PDF, RTF, MS Word, Excel, PowerPoint, Audio or Video files, see Help Downloading Files.