GENOMIC SEQUENCING AND NEWBORN SCREENING DISORDERS

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In the beginning...
...and in the more recent past!
To prepare for these changes and the impact that it might have on newborn screening and child health, Alan Guttmacher and Eric Green brought together staff members with the intention of organizing a workshop to discuss these concerns...
The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), the National Human Genome Research Institute (NHGRI), and the NIH Office of Rare Diseases Research (ORDR) sponsored a workshop, *Newborn Screening in the Genomic Era: Setting a Research Agenda*. 

The purpose of the meeting was to identify elements of a trans-NIH research agenda that would lead to the application of new genomics concepts and technologies to newborn screening and child health.

The meeting was attended by experts from academia, industry, and federal agencies in the fields of newborn screening (NBS) and genomics.

Chaired by Drs. David Valle (Johns Hopkins, University) and Piero Rinaldo (Mayo Clinic).
NEWBORN WORKSHOP DECEMBER 2010

- Goal to set research agenda
- Potential first adopters
- Near-universal inclusion
- Lifetime personalized medicine
- Pilot studies - First step
- Newborn screening = current public health program
- Screening of newborns = using sequencing to screen newborns for multiple conditions
PRIMARY OUTCOMES OF THE PROCEEDINGS

• Important to evaluate genomic data in newborns using newborn screening as a framework
• Important prioritize clinical validity and clinical utility; not just analytical validity
• Important to address ethical, legal and social concerns
### Department of Health and Human Services

#### Part 1. Overview Information

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<tr>
<th>Participating Organization(s)</th>
<th>National Institutes of Health (NIH)</th>
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| 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 |
| Funding Opportunity Announcement (FOA) Number | RFA-HD-13-010 |
MUST ADDRESS ONE OR MORE OF THE FOLLOWING 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 clinical care of newborns?
EMPHASIS & QUALITY OF PROJECTS MUST BE EQUAL

- Genomic Data Sets
- Clinical Research
- Ethical, Legal & Social
METHODS DEVELOPMENT FOR OBTAINING COMPREHENSIVE GENOMIC INFORMATION FROM HUMAN SPECIMENS THAT ARE EASY TO COLLECT AND STORE (R43/R44)
PAR-13-203: OBJECTIVES

To develop sensitive technologies or methods for obtaining high quality and comprehensive nucleic acids-based genomic data from limited quantities of human specimens that are easy to collect, handle, and store.
PAR-13-203: REVIEW CRITERIA

1. Ease of proposed sample collection methods at least comparable to that of the current dried blood spot collection method

2. Genomic data obtained at least equivalent to that which can be obtained from fresh whole blood in quality and comprehensiveness
PAR-13-203: DATES AND FUNDS

R43/R44 Small Business Innovation Research (SBIR) Grant - Phase I, Phase II, and Fast-Track

Application Due Dates:

• March, July, and December
• July 2013 – March 2016
• Next Dec 2nd 2013

Funding support may not exceed $225,000 for Phase I awards and $1,500,000 for Phase II awards in total costs.
RESOURCES + OTHER FOAs
One Hundred Tenth Congress
of the
United States of America

AT THE SECOND SESSION

Began and held at the City of Washington on Thursday,
the third day of January, two thousand and eight

An Act

To amend the Public Health Service Act to establish grant programs to provide for education and outreach on newborn screening and coordinated follow-up care once newborn screening has been conducted, to reauthorize programs under part A of title XI of such Act, and for other purposes.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

SECTION 1. SHORT TITLE.

This Act may be cited as the “Newborn Screening Saves Lives Act of 2007.”

SEC. 2. IMPROVED NEWBORN AND CHILD SCREENING FOR HERITABLE DISORDERS.

Section 1109 of the Public Health Service Act (42 U.S.C. 300b–8) is amended—

(1) by striking subsections (a), (b), and (c) and inserting the following:

“(a) AUTHORIZATION OF GRANT PROGRAM.—From amounts appropriated under subsection (j), the Secretary, acting through the Administrator of the Health Resources and Services Administration (referred to in this section as the ‘Administrator’) and in consultation with the Advisory Committee on Heritable Disorders in Newborns and Children (referred to in this section as the ‘Advisory Committee’), shall award grants to eligible entities to enable such entities—

“(1) to enhance, improve or expand the ability of State and local public health agencies to provide screening, counseling, or health care services to newborns and children having or at risk for heritable disorders;

“(2) to assist in providing health care professionals and newborn screening laboratory personnel with education in newborn screening and training in relevant and new technologies in newborn screening and congenital, genetic, and metabolic disorders;

“(3) to develop and deliver educational programs (at appropriate literacy levels) about newborn screening counseling, testing, follow-up, treatment, and specialty services to parents, families, and patient advocacy and support groups; and

“(4) to establish, maintain, and operate a system to assess and coordinate treatment relating to congenital, genetic, and metabolic disorders.

“(b) ELIGIBLE ENTITY.—In this section, the term ‘eligible entity’ means—

“(1) a State or a political subdivision of a State;
GOALS OF THE HUNTER KELLY NEWBORN SCREENING RESEARCH PROGRAM AT THE NIH

Identify, develop and test the most promising new screening technologies

Increase the specificity of newborn screening and expand the number of conditions for which screening tests are available

Develop experimental treatments and disease management strategies for additional newborn conditions, and other genetic, metabolic, hormonal and or functional conditions that can be detected through newborn screening for which treatment is not yet available.
Newborn Screening Translational Research Network (NBSTRN)

- Primary Aim is to develop a research infrastructure to support investigators with projects related to newborn screening
  - Awarded Sept. 2008
  - American College of Medical Genetics
  - 5 years
NBSTRN UPDATE

**R4S**
- Analytical and clinical validation
- Laboratory protocols, definitions

**Virtual Repository of Dried Blood Spots - VRDBS**
- Search and request de-identified residual dried blood spots
- Secure research support and request management

**LPDR**
- Secure, standards-based clinical data collection and management
- Aggregate, share, and analyze data
Find all types of GTR records, including tests, conditions/phenotypes, genes, and labs.

You Tube GTR Tutorials

IMPORTANT NOTE: NIH does not independently verify information submitted to the GTR; it relies on submitters to provide information that is accurate and not misleading. NIH makes no endorsements of tests or laboratories listed in the GTR. GTR is not a substitute for medical advice. Patients and consumers with specific questions about a genetic test should contact a health care provider or a genetics professional.

GENETIC TESTING REGISTRY

The Genetic Testing Registry (GTR) provides a central location for voluntary submission of genetic test information by providers. The scope includes the test's name, methodology, validity, evidence of the test's usefulness, and laboratory names and credentials. The overarching goal of the GTR is to advance the public's understanding and research into the genetic basis of health and disease.

GeneReviews

OMIM

Orphanet

NHGRI Talking Glossary

Expert-authored summaries about diagnosis, management and genetic counseling for specific inherited conditions, University of Washington. NCBi's Bookshelf: GeneReviews Advanced Search

Online Mendelian Inheritance in Man: A Catalog of Human Genes and Genetic Disorders, Johns Hopkins University.

Portal for information about rare diseases and orphan drugs, led by a European consortium.

Expert description of genetic terms and concepts, images, animation and links.
Fragile X syndrome

SNOMED CT: Fragile X syndrome, ID: 613003
Synonyms: FMR1-Related Disorders, FRAGILE X MENTAL RETARDATION SYNDROME, Fra(X) syndrome, Fragile X syndrome, type A, MENTAL RETARDATION, X-LINKED, ASSOCIATED WITH marXq28, Marker X syndrome, Martin-Bell syndrome, X-linked mental retardation and macroorchidism

Disease characteristics

FMR1-related disorders include fragile X syndrome, fragile X-associated tremor/ataxia syndrome (FXTAS), and FMR1-related primary ovarian insufficiency (POI). Fragile X syndrome occurs in individuals with an FMR1 full mutation or other loss-of-function mutation and is nearly always characterized by moderate intellectual disability in affected males and mild intellectual disability in affected females. Because FMR1 mutations are complex alterations involving non-classic gene-disrupting alterations (trinucleotide repeat expansion) and abnormal gene methylation, affected individuals occasionally have an atypical presentation with an IQ above 70, the traditional demarcation denoting intellectual disability (previously referred to as mental retardation). Males with an FMR1 full mutation accompanied by aberrant methylation may have a characteristic appearance (large head, long face, prominent forehead and chin, protruding ears), connective tissue findings (joint laxity), and large testes after puberty. Behavioral abnormalities, sometimes including autism spectrum disorder, are common. FXTAS occurs in males (and some females) who have an FMR1 premutation and is characterized by late-onset, progressive cerebellar ataxia and intention tremor. FMR1-related POI (age at cessation of menses <40 years) occurs in approximately 20% of females who have an FMR1 premutation.

Full text of GeneReview (by section):

Summary | Diagnosis | Clinical Description | Differential Diagnosis | Management | Genetic Counseling | Resources | Molecular Genetics | References

Chapter Notes

Authors:
Robert A Saul | Jack C Tarleton

view full author information
Available tests

**Clinical tests** (151 available)

Biochemical Genetics Tests
- Protein analysis (1)
- Analyte (1)

Cytogenetics Tests
- FISH-metaphase (1)

Molecular Genetics Tests
- Targeted mutation analysis (135)
- Microsatellite instability testing (MSI) (2)
- Methylation analysis (68)
- Linkage analysis (6)
- Sequence analysis of the entire coding region (14)
- Deletion/duplication analysis (15)

Research tests
- See all research tests for this condition (3)

Associated genes

**FMR1**  see tests for this gene

Also known as: FMRP, FRAXA, POF, POF1
Summary: fragile X mental retardation 1

Related conditions
The Undiagnosed Diseases Network (UDN) is being established across the country to increase the capacity for and use of genomic data in the diagnosis of rare and new diseases. The Network also hopes to aid in management strategies for patients with such disorders.
UNDIAGNOSED DISEASES NETWORK

Undiagnosed Diseases Program (UDP)

Coordinating Center (RM-12-020)

Clinical Sites (RM-13-004)

Gene Function Studies (PA-13-076, RM-13-003)

DNA Seq Core (RM-13-018)
Aim: Establish a DNA sequencing core for patients seen through the NIH Undiagnosed Diseases Network.

Objectives of this program are to:
1. Provide DNA sequencing and CLIA variant validation
2. Provide raw sequence results as quickly as possible within at most a two-week turnaround time
3. Participate in the network-wide mission
The **Centers for Mendelian Genomics** apply sequencing and computational approaches to discover the genes and variants that underlie Mendelian conditions.

If you are interested in working with the CMG to discover the genetic basis for a Mendelian condition, please contact: [gmendel@mendelian.org](mailto:gmendel@mendelian.org)

To submit a Mendelian disorder for sequencing, please visit [PhenoDB](https://cmg-phenodb.mendelian.org/), to create an account:
The Encyclopedia Of DNA Elements (ENCODE) Project aims to identify all functional elements in the human genome sequence.

Tutorials on using the ENCODE Project data can be found at:

http://www.genome.gov/27553900
http://encodeproject.org/ENCODE/usageResources.html