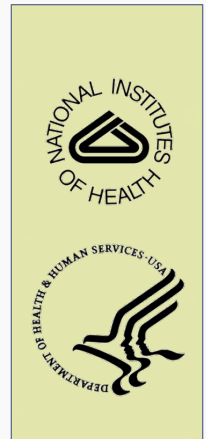
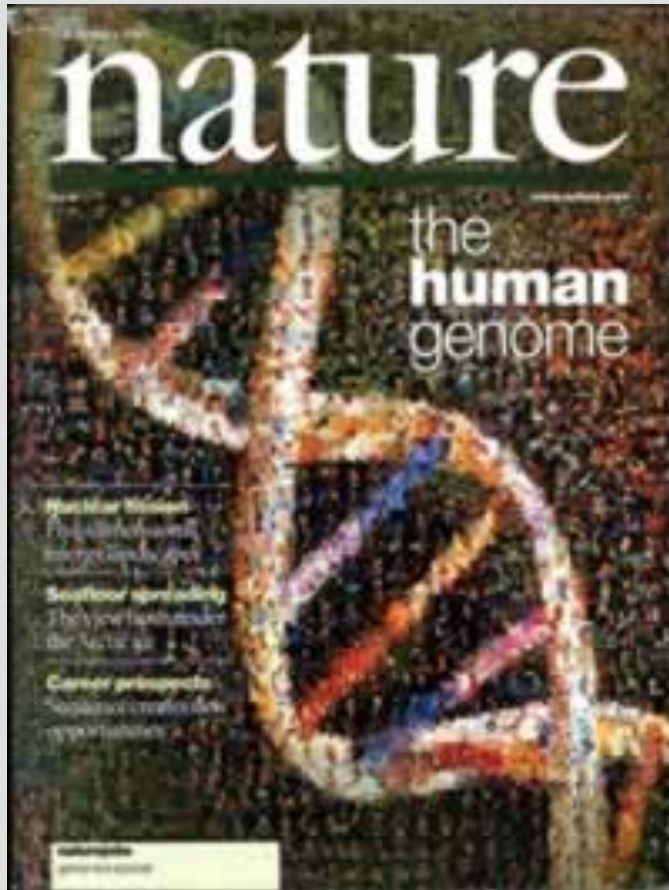


GENOMIC SEQUENCING AND NEWBORN SCREENING DISORDERS

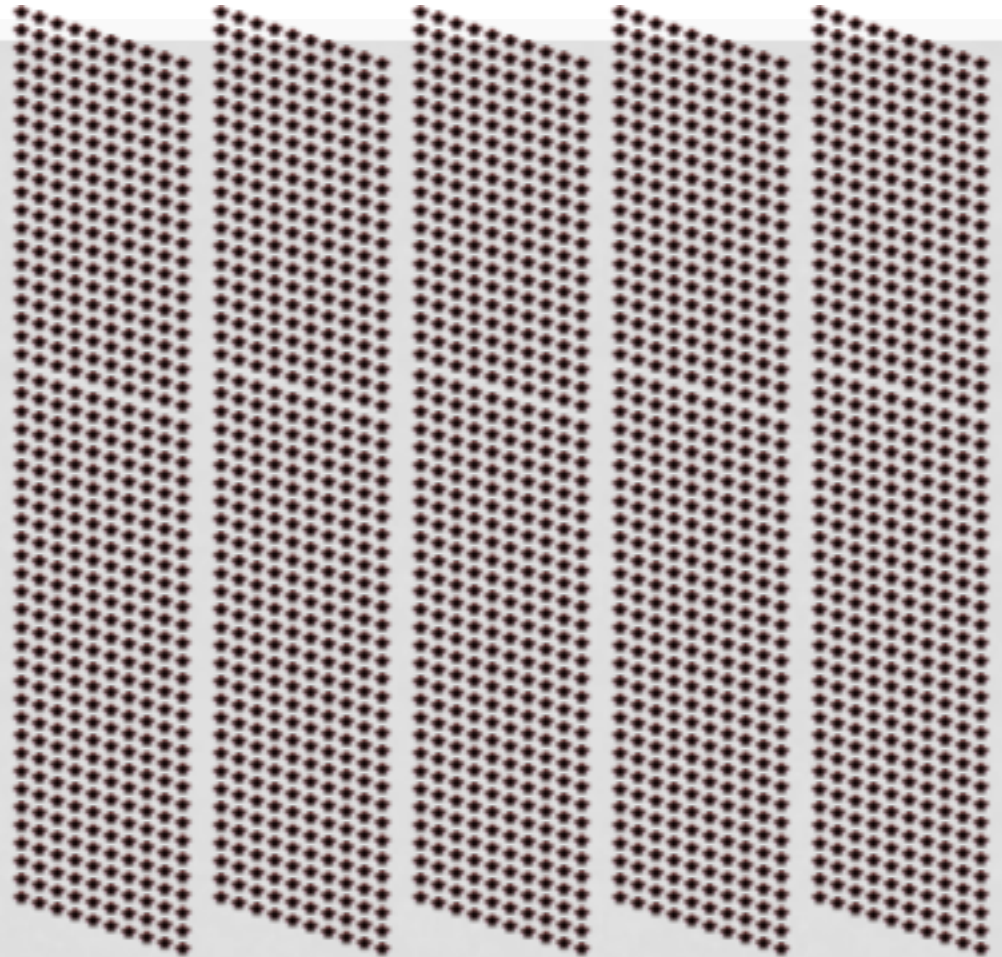
TIINA K. URV, PH.D. NICHD
ANASTASIA WISE, PH.D. NHGRI



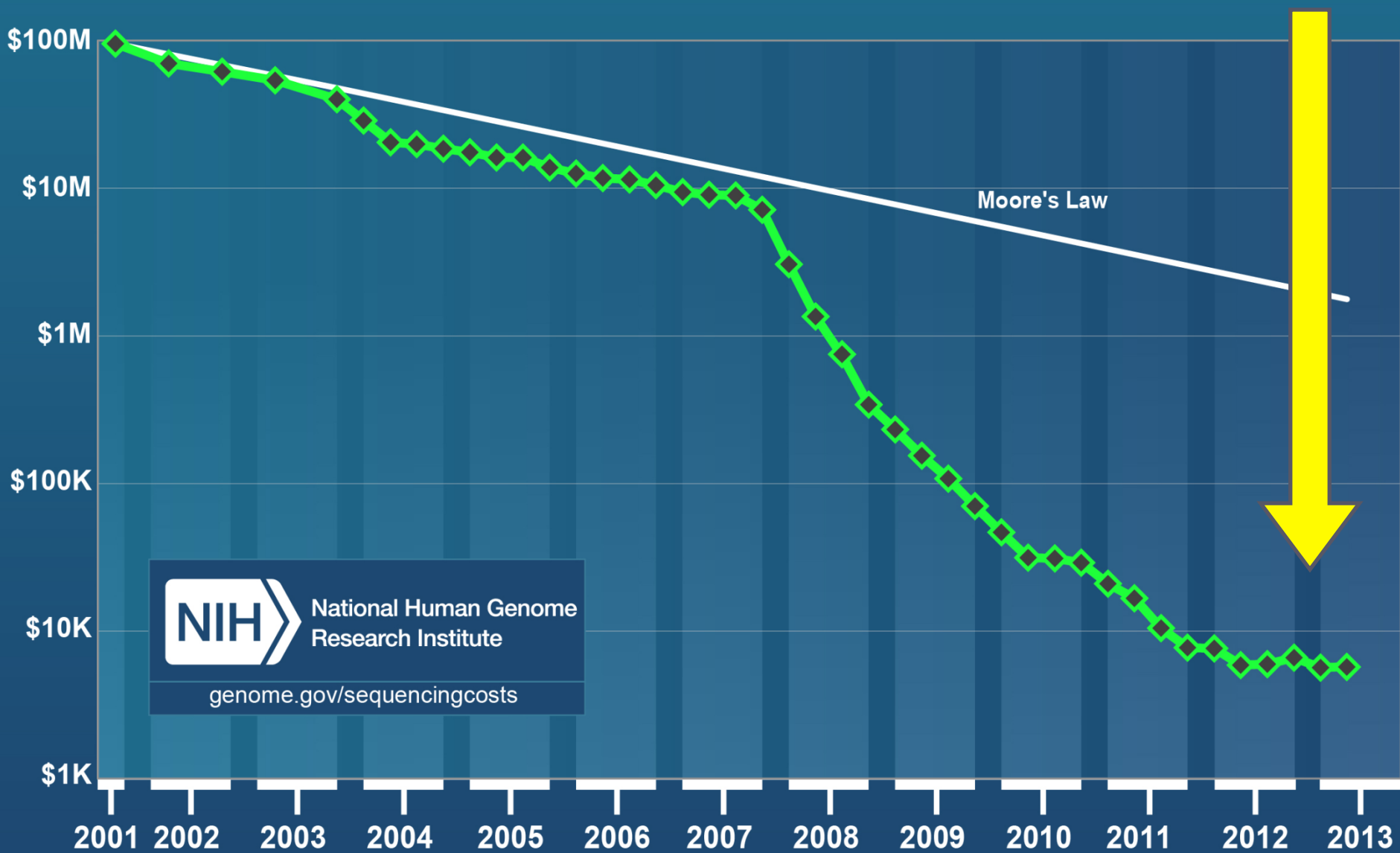
In the beginning...



...and in the more recent past!



Cost per Genome





NEWBORN SCREENING IN THE GENOMIC ERA: SETTING A RESEARCH AGENDA



5635 Fishers Lane, Rockville, MD
December 13–14, 2010

SPONSORED BY:

Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)
National Human Genome Research Institute (NHGRI)
NIH Office of Rare Diseases Research (ORDR)



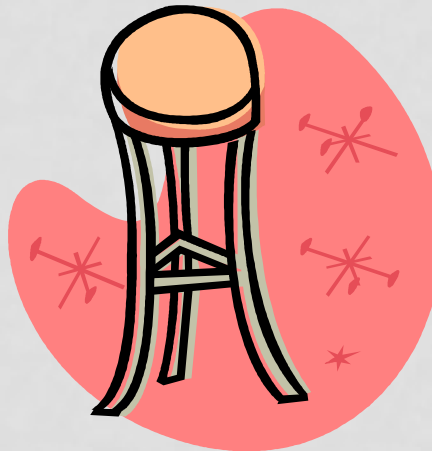
- The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), the National Human Genome Research Institute (NHGRI), and the NIH Office of Rare Diseases Research (ORDR) sponsored a workshop, *Newborn Screening in the Genomic Era: Setting a Research Agenda*.
- The purpose 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 to prioritize clinical validity and clinical utility; not just analytical validity
- Important to address ethical, legal and social concerns




Department of Health and Human Services

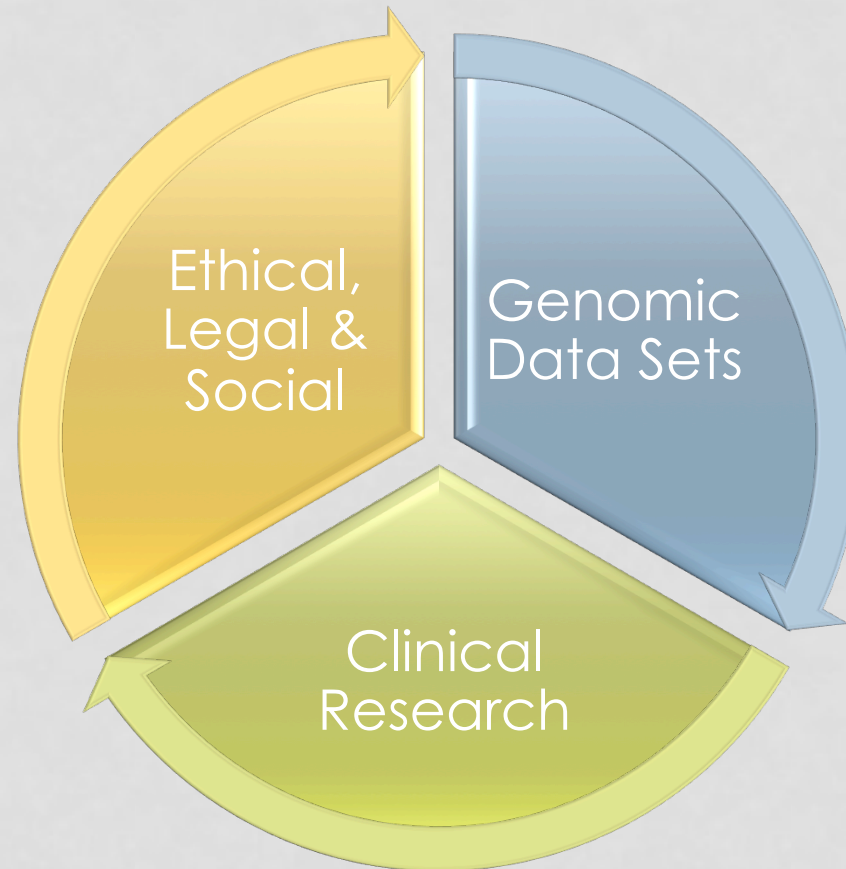
Part 1. Overview Information

Participating Organization(s)	National Institutes of Health (NIH)
Components of Participating Organizations	<i>Eunice Kennedy Shriver</i> 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	<ul style="list-style-type: none">• August 15, 2012 - Informational/Technical Assistance Pre-application Meeting for RFA-HD-13-010. See Notice NOT-HD-12-027.
Funding Opportunity Announcement (FOA) Number	RFA-HD-13-010

MUST ADDRESS ONE OR MORE OF THE FOLLOWING QUESTIONS

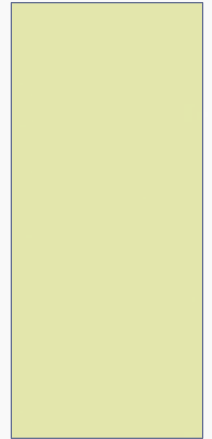
- 
- For disorders currently screened for in newborns, how can genomic sequencing replicate or augment known newborn screening results?
 - What knowledge about conditions not currently screened for in newborns could genomic sequencing of newborns provide?
 - What additional clinical information could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

EMPHASIS & QUALITY OF PROJECTS MUST BE EQUAL



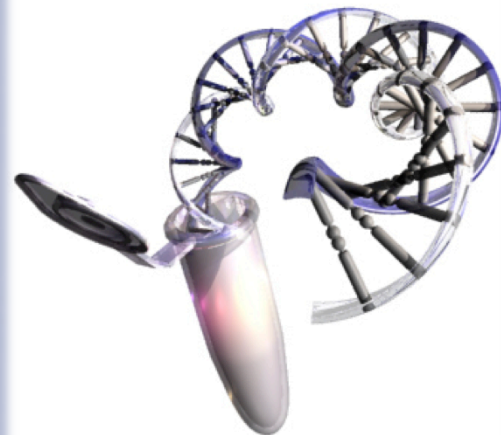
METHODS DEVELOPMENT FOR OBTAINING
COMPREHENSIVE GENOMIC INFORMATION FROM
HUMAN SPECIMENS THAT ARE EASY TO COLLECT
AND STORE (R43/R44)

PAR-13-203



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.



National Institutes of Health
Turning Discovery Into Health

RESOURCES + OTHER FOAs

One Hundred Tenth Congress
of the
United States of America

AT THE SECOND SESSION

*Begun 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 followup 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 DISORDER.

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;

THE NEWBORN SCREENING SAVES LIVES ACT OF 2007

...The Secretary, in
conjunction with the Director
of the Centers for Disease Control and
Prevention, shall consider
recommendations of the
Advisory Committee and may
continue carrying out,
coordinating, and expanding
research in newborn
screening...



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.



N B S T R N

NEWBORN
SCREENING
TRANSLATIONAL
RESEARCH
NETWORK

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

NEWBORN SCREENING TRANSLATIONAL RESEARCH NETWORK

Welcome to the Newborn Screening Domain



MS/MS

Amino Acids & Acylcarnitines by MS/MS



SCID

Severe Combined Immunodeficiency



LSD

Lysosomal Storage Disorders

R4S

- Analytical and clinical validation
- Laboratory protocols, definitions

Dried Blood Spots

Research Support Search

NEWBORN
SCREENING
TRANSLATIONAL
RESEARCH
NETWORK

REQUEST DRIED BLOOD SPOTS FOR

Search and request de-identified residual dried blood spots (DBS) to use in newborn screening research projects.

Register Now

Learn More

Privacy Policy

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

GENETIC TESTING REGISTRY

All GTR

Tests

Conditions/Phenotypes

Genes

Labs

GeneReviews

Search All GTR

Find all types of GTR records, including tests, conditions/phenotypes, genes, and labs.

You  [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.

GTR

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 location and credentials. The overarching goal of the GTR is to advance the public understanding and research into the genetic basis of health and disease.

[Director Dr. Francis Collins blogs about GTR](#)

[How to use GTR](#)

[Learn about GTR](#)

[News](#) 

[Information at NIH Office of the Director](#)

[Engage in the Community](#)

[Contact GTR and provide feedback](#)

Clinical Resources

[GeneReviews](#)

Expert-authored summaries about diagnosis, management and genetic counseling for specific inherited conditions, University of Washington. NCBI's Bookshelf: [GeneReviews Advanced Search](#)

[OMIM](#)

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

[Orphanet](#)

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

[NHGRI Talking Glossary](#)

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

fragile x syndrome

Conditions/Phenotypes

Search

[GTR Home](#) > [Conditions/Phenotypes](#) > Fragile X syndrome

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

Excerpted from the *GeneReview*: [FMR1-Related Disorders](#)

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

154 tests are in the database for this condition. [Compare labs offering these tests](#)

Check [Associated genes](#) and [Related conditions](#) for additional relevant 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

C Clinical test, **R** Research test, **O** OMIM, **G** GeneReviews

UNDIAGNOSED DISEASES NETWORK

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.



National Institutes of Health
Office of Strategic Coordination - The Common Fund

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)**

UNDIAGNOSED DISEASES NETWORK

RFA-RM-13-018 "DNA Sequencing Core for an Undiagnosed Diseases Network (UDN) (U01)"

Applications Due: **November 19, 2013**

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

Centers for Mendelian Genomics

Finding the genes underlying human Mendelian conditions

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

To submit a Mendelian disorder for sequencing, please visit **PhenoDB**, to create an account:

[**https://cmg-phenodb.mendelian.org/**](https://cmg-phenodb.mendelian.org/)



ENCODE TUTORIALS

The **Enc**yclopedia **Of** **DNA** **E**lements (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>