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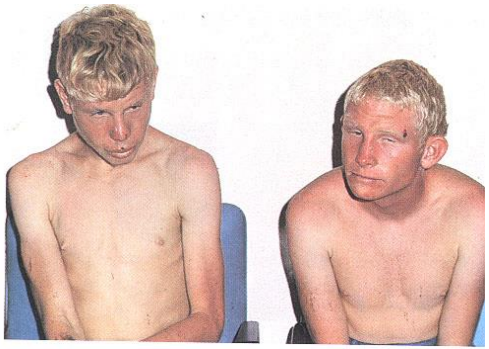
Newborn Screening: History and Molecular Overview

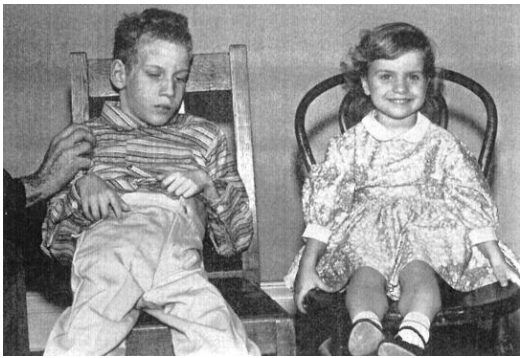
Michele Caggana, Sc.D., FACMG

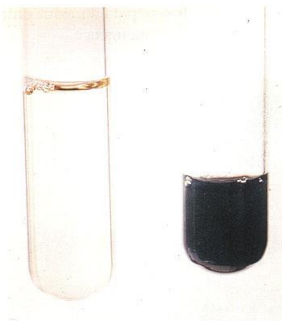
APHL/CDC Molecular Workshop

February 24, 2020

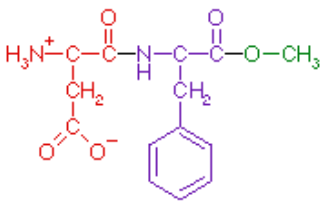
First – History of Phenylketonuria







Phenylpyruvic acid
FeCl3 test



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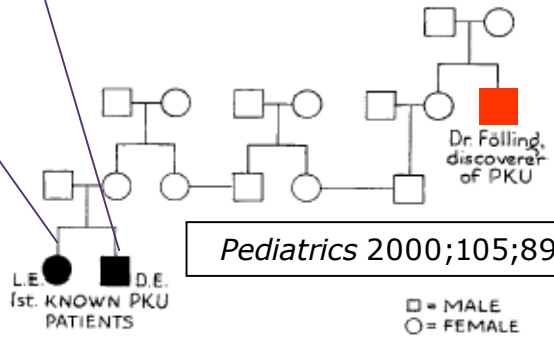
http://138.192.68.68/bio/Courses/biochem2/AminoAcids/AminoAcidCarbonDeg.html

Asbjorn Folling

Liv

Dag

Borgny and Harry Egeland



Pediatrics 2000;105;89-103

Fig 6. The relationship between Dr Fölling and the children first discovered to have PKU—a chance relationship through marriage and not genetically related.

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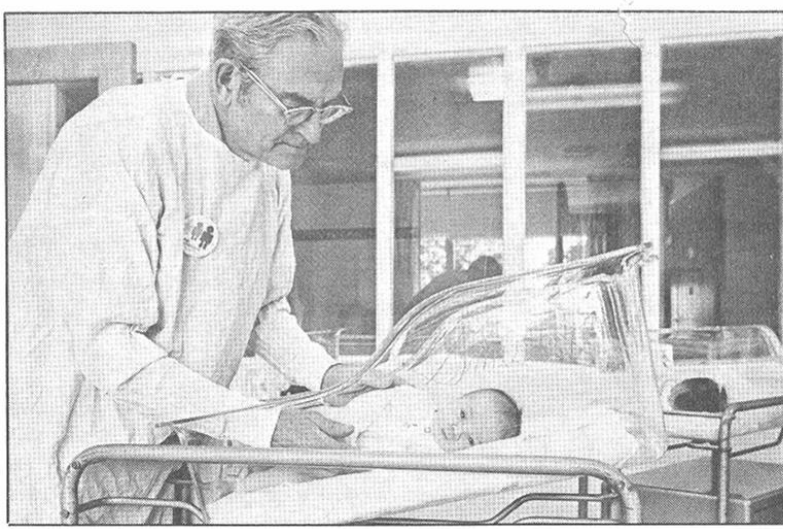
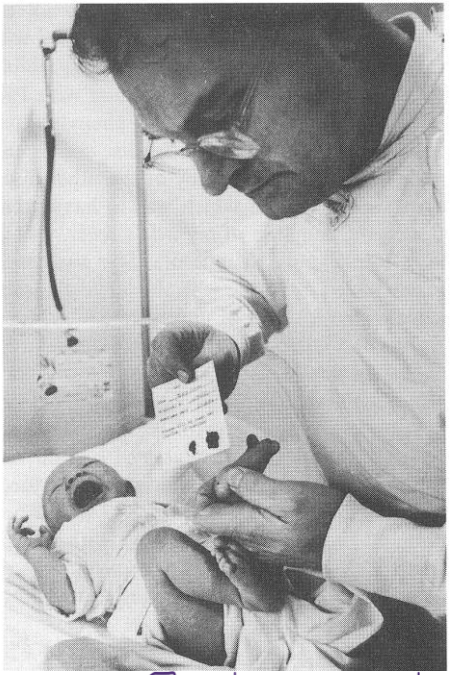
Two Interests

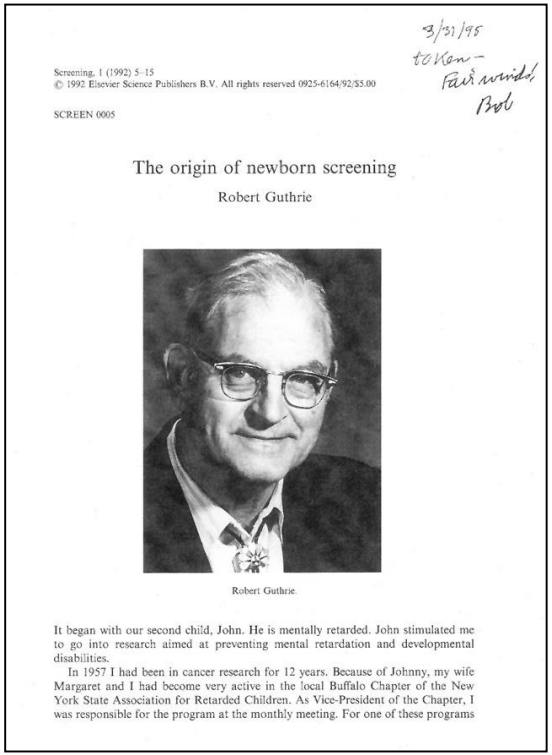




Niece had PKU; son with intellectual disability

Pictures Courtesy of Dr. Kenneth Pass

Jamestown, New York



3/31/95
to Ken –
Fair winds!
Bob

Screening, 1 (1992) 5–15

SCREEN 0005

The origin of newborn screening

Robert Guthrie

Robert Guthrie

It began with our second child, John. He is mentally retarded. John stimulated me to go into research aimed at preventing mental retardation and developmental disabilities.

In 1957 I had been in cancer research for 12 years. Because of Johnny, my wife Margaret and I had become very active in the local Buffalo Chapter of the New York State Association for Retarded Children. As Vice-President of the Chapter, I was responsible for the program at the monthly meeting. For one of these programs

Picture Courtesy of Dr. Kenneth Pass

- **Fall 1961 talk for The Association for Retarded Children**
- **Began to receive newborn filter-paper specimens (29 states; 400K babies**
- **“Thus, screening had its start in Jamestown, New York in 1961”**

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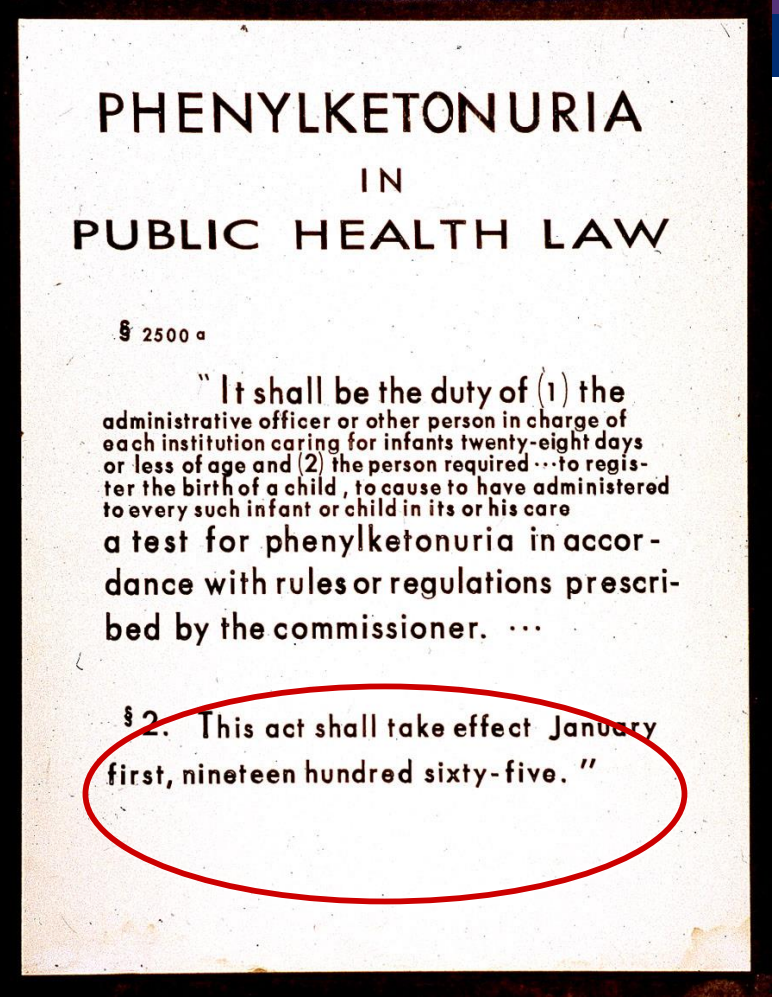


PHENYLKETONURIA

IN

PUBLIC HEALTH LAW

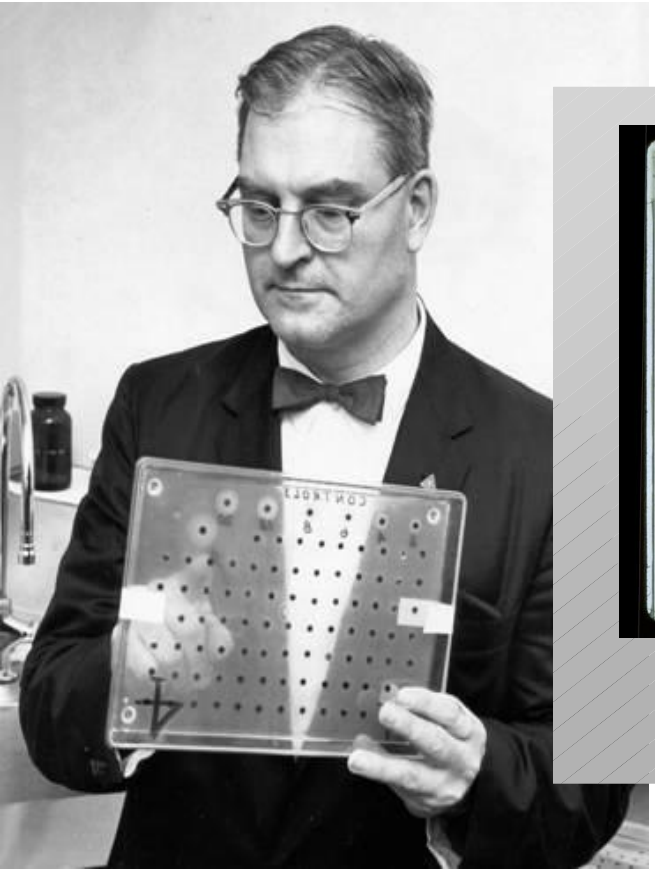
§ 2500 a

"It shall be the duty of (1) the administrative officer or other person in charge of each institution caring for infants twenty-eight days or less of age and (2) the person required ··· to register the birth of a child, to cause to have administered to every such infant or child in its or his care a test for phenylketonuria in accordance with rules or regulations prescribed by the commissioner. ···

§ 2. This act shall take effect January first, nineteen hundred sixty-five."

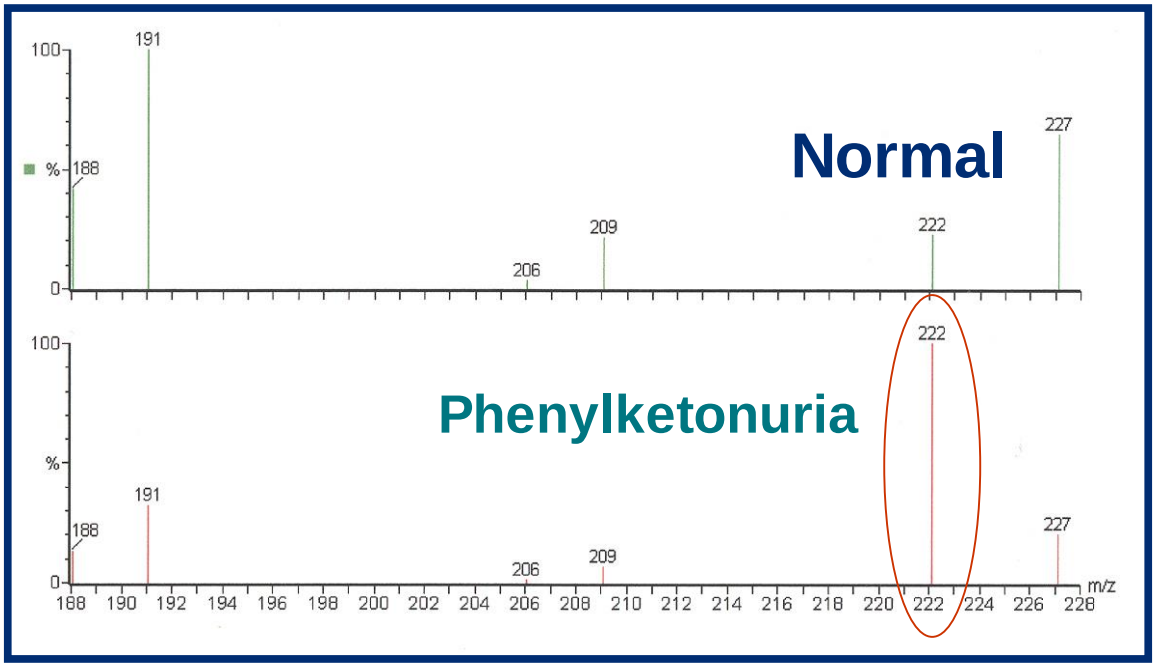
Part 69

Duties of birth hospitals, CEOs, physicians, Midwives (birth attendants) and Specialty Care Center Directors




Acquity
Acquity
Acquity

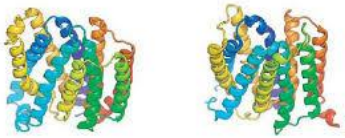
MS/MS Phenylketonuria

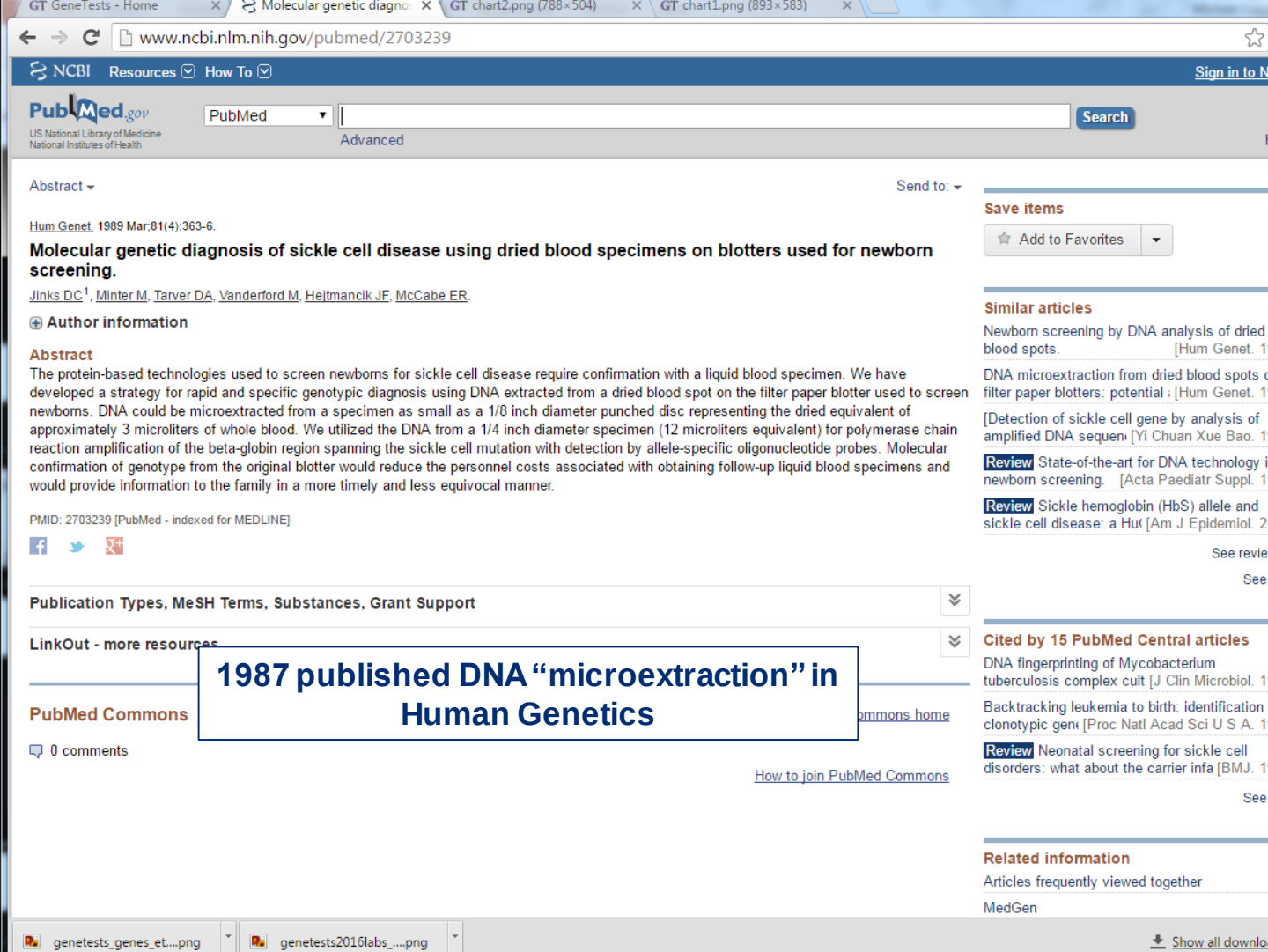


Data from Dr. Mark Morrissey

Adenine -- purine
Thymine -- pyrimidine
Cytosine -- pyrimidine
Guanine -- purine

46 chromosomes
3 billion bases
2 meters long
21 amino acids

RNA →  **Protein**


GT GeneTests - Home
Molecular genetic diagno
GT chart2.png (788×504)
GT chart1.png (893×583)
www.ncbi.nlm.nih.gov/pubmed/2703239
NCBI Resources How To
Sign in to N
PubMed.gov
US National Library of Medicine
National Institutes of Health
PubMed
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Abstract
Send to:
Hum Genet. 1989 Mar;81(4):363-6.
Molecular genetic diagnosis of sickle cell disease using dried blood specimens on blotters used for newborn screening.
Jinks DC[1], Minter M, Tarver DA, Vanderford M, Hejtmancik JF, McCabe ER.
Author information
Abstract
The protein-based technologies used to screen newborns for sickle cell disease require confirmation with a liquid blood specimen. We have developed a strategy for rapid and specific genotypic diagnosis using DNA extracted from a dried blood spot on the filter paper blotter used to screen newborns. DNA could be microextracted from a specimen as small as a 1/8 inch diameter punched disc representing the dried equivalent of approximately 3 microliters of whole blood. We utilized the DNA from a 1/4 inch diameter specimen (12 microliters equivalent) for polymerase chain reaction amplification of the beta-globin region spanning the sickle cell mutation with detection by allele-specific oligonucleotide probes. Molecular confirmation of genotype from the original blotter would reduce the personnel costs associated with obtaining follow-up liquid blood specimens and would provide information to the family in a more timely and less equivocal manner.
PMID: 2703239 [PubMed - indexed for MEDLINE]
Publication Types, MeSH Terms, Substances, Grant Support
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[Detection of sickle cell gene by analysis of amplified DNA sequen [Yi Chuan Xue Bao. 1
Review State-of-the-art for DNA technology newborn screening. [Acta Paediatr Suppl. 1
Review Sickle hemoglobin (HbS) allele and sickle cell disease: a Hu [Am J Epidemiol. 2
See revie
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Cited by 15 PubMed Central articles
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Backtracking leukemia to birth: identification clonotypic gen [Proc Natl Acad Sci U S A. 1
Review Neonatal screening for sickle cell disorders: what about the carrier infa [BMJ. 1
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Related information
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1987 published DNA "microextraction" in Human Genetics
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Chronology of NBS

- 1957 Diaper Test for PKU in California
- 1958 Phenistix Used in Europe
- 1963 Guthrie and Susi – Bacterial Inhibition Assay
- 1964 Universal Screening in Massachusetts
- 1978 Radioimmunoassay Introduced
- 1994 MS / MS Used
- 1994 Molecular in Washington (2002 in NY)

Human Genome Project

- Proposed by Victor McKusick in 1968
- *(when did newborn screening start)????*
- DOE and NIH, 15 years, 30 billion dollars
- James Watson original head then Francis Collins
- International effort
- ELSI budget

Human Genome Project

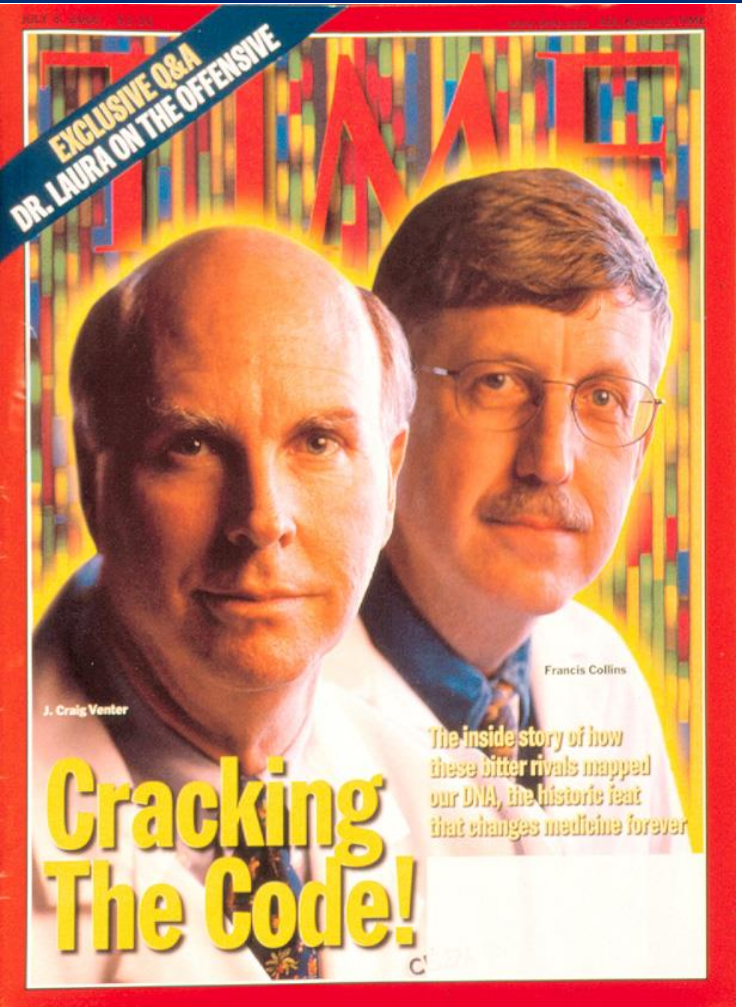
Five Main Objectives:

1. Generate genetic and physical maps
2. Develop new DNA technologies
3. Accurately sequence the human genome
4. Develop informatics
5. Sequence model organisms

Human Genome Project

Accurate Sequence Data:

- 3,000,000,000 bases; haploid
- Rough draft / 90%, summer 2000, 2/01 "finished"
- Highly accurate (1 error in 100,000 bases) no gaps or ambiguities by 2003
- First chromosome 22 reported 12/99 – why? chromosome 21 reported 5/00
- Projected finish 2003, original 2005



Venter & Collins

Private vs. Public

1000 Genomes Project

http://www.1000genomes.org/

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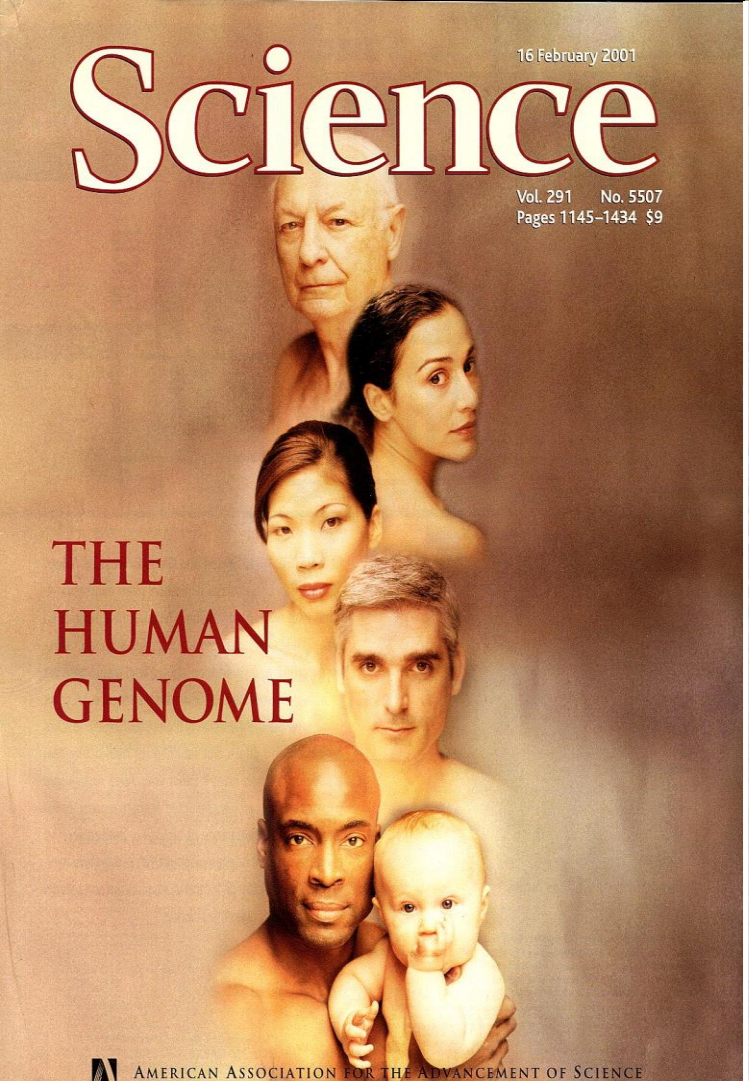
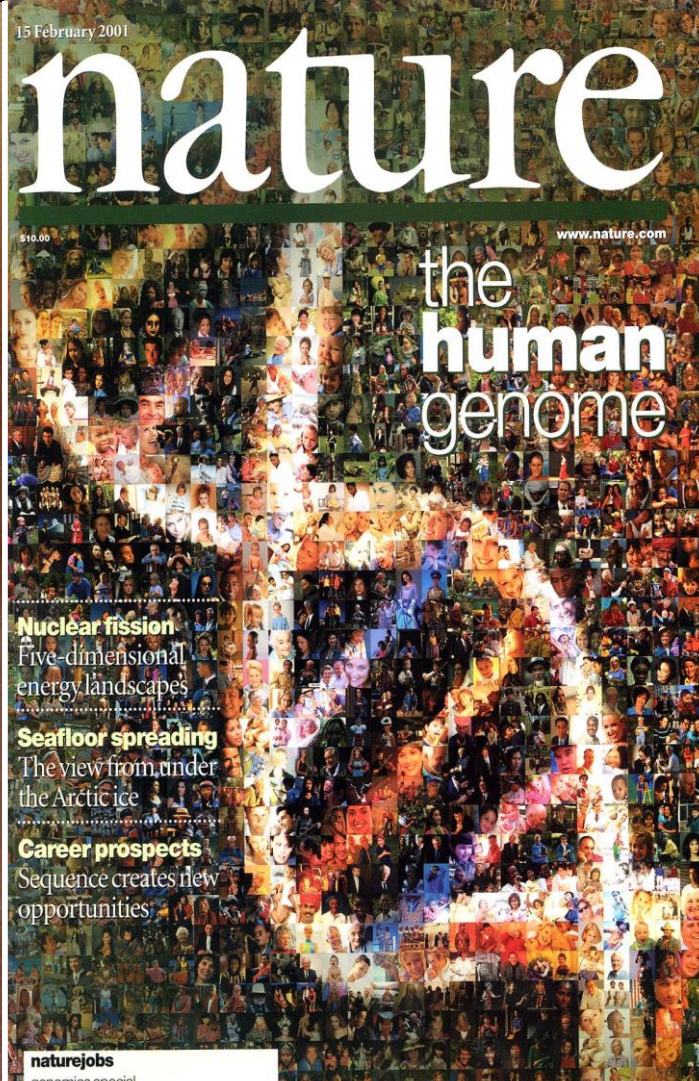

Science
16 February 2001
Vol. 291 No. 5507
Pages 1145–1434 $9
THE HUMAN GENOME
AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE


15 February 2001
nature
$10.00
www.nature.com
the human genome
Nuclear fission
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The view from under the Arctic ice
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Genetic Disorders

- **Caused by pathogenic variants* in genes or chromosomes**
- **Pathogenic variants may occur on:**
  - **-- An autosome (autosomal)**
  - **-- A sex chromosome (X-linked or Y-linked)**
  - **-- Multiple genes**
- **Disease expression may be impacted by environmental factors (multifactorial)**

**Used to be mutations!*

Single Gene Disorders

- Caused by pathogenic variants in one gene
- Generally follow Mendelian inheritance patterns

  -- Dominant vs. Recessive

  -- Expression may be impacted by genomic imprinting or penetrance
- Includes most inborn errors of metabolism [autosomal recessive]

Most "single gene disorders" are probably influenced by multiple genes, so-called modifiers; also epigenetic changes

Classes of Single Gene Disorders

Autosomal Dominant

- One copy of a gene must be altered to be affected
  - aka: AA or Aa
  - Heterozygous and homozygous individuals are affected
  - e.g. achondroplasia, Huntington disease

Autosomal Recessive

- Both copies of the gene must be altered to be affected
  - aka: aa
  - Only individuals with variants on both chromosomes are affected.
  - e.g. Sickle cell anemia, cystic fibrosis, galactosemia (NBS)

Autosomal Dominant

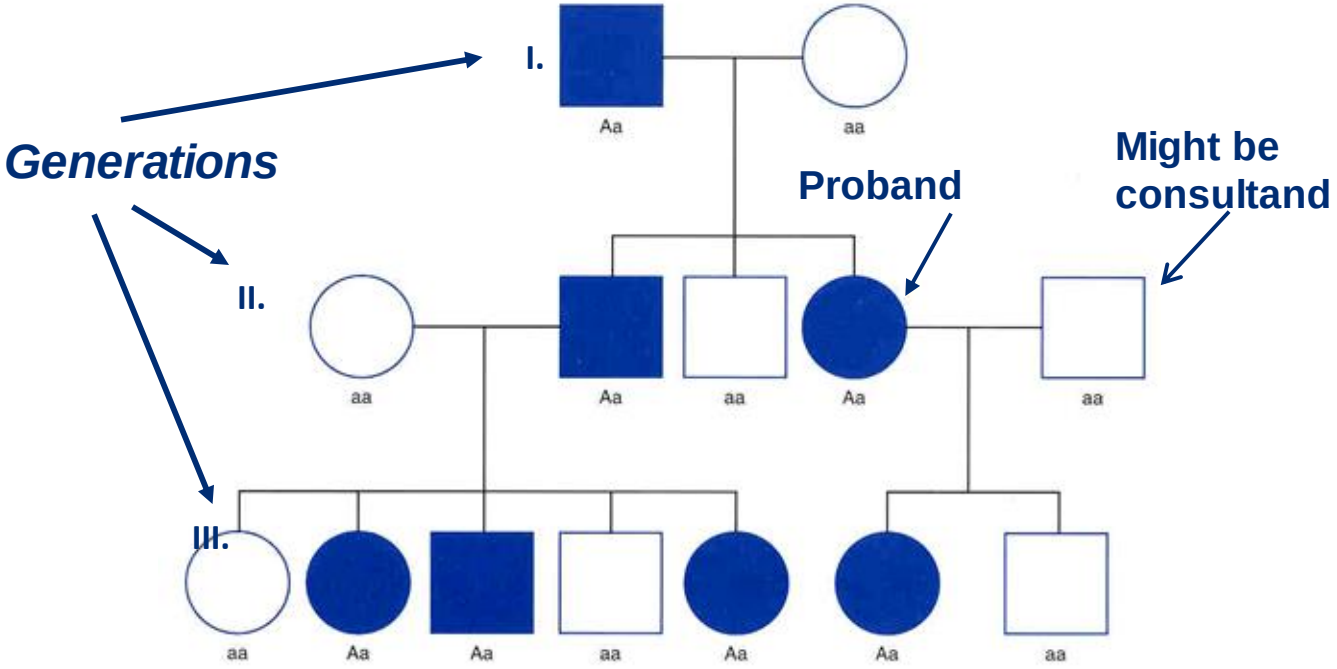
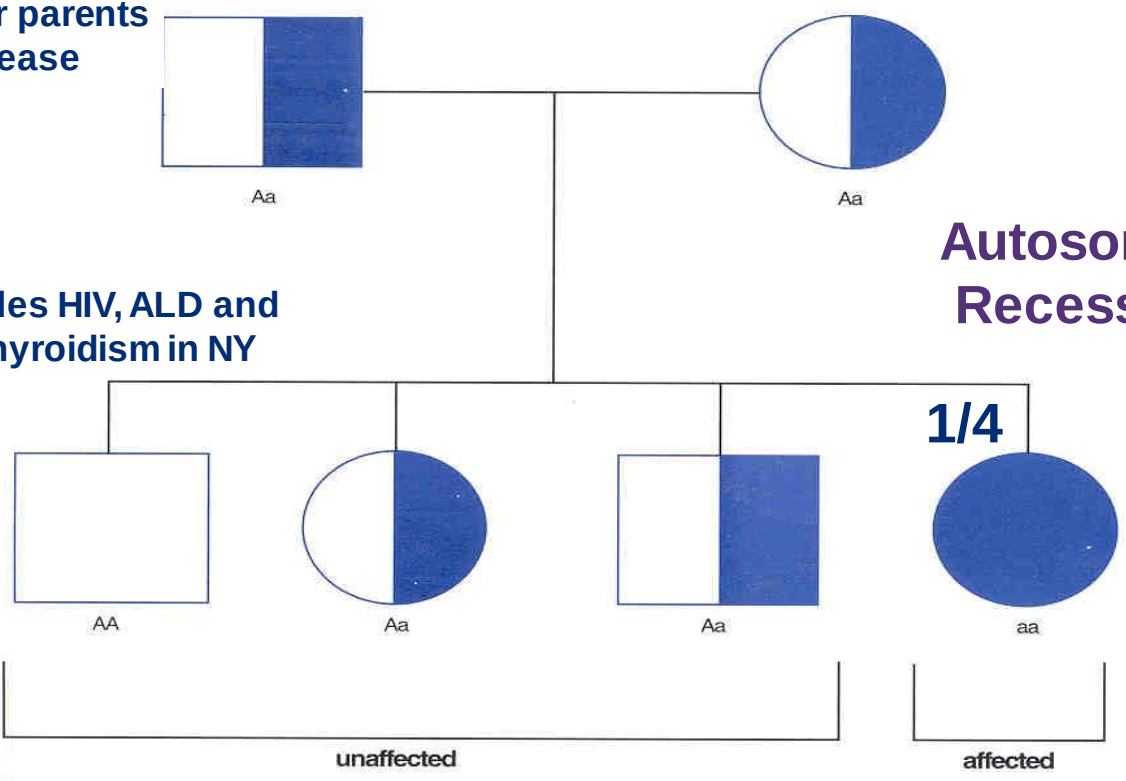


FIGURE 2-5 Pedigree illustrating autosomal dominant transmission. The dominant allele *A* is passed from generation to generation.

Human Genetics, Korf, 1996

"A" is the altered allele

Carrier parents
No disease



Autosomal Recessive

Excludes HIV, ALD and hypothyroidism in NY

FIGURE 1-8 Pedigree illustrating segregation of autosomal recessive trait. Allele *A* is dominant, *a* is recessive.

Human Genetics, Korf, 1996

Classes of Single Gene Disorders

X-linked Recessive

- -- Males affected if X chromosome is altered
- -- Females affected only if both X chromosomes are altered; e.g. Duchenne muscular dystrophy & hemophilia and ALD

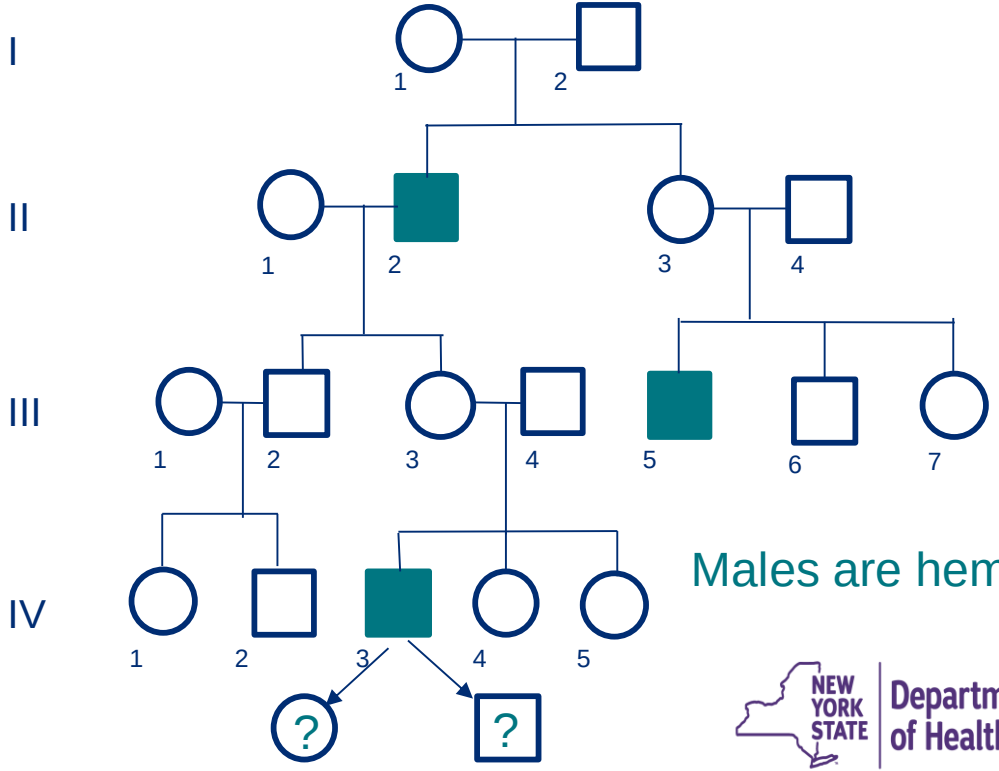
X-linked Dominant

- -- Individuals with 1 altered copy of X chromosome are affected; e.g. Rett syndrome

Y-linked

- -- Individuals with an altered Y chromosome are affected
- -- Rare

Inheritance Type: X-Linked Recessive Inheritance



Males are hemizygous

Molecular Testing for Genetic Diseases

- **Enabled by gene mapping to identify location of genes on chromosomes AND ability to differentiate between harmful and neutral variants**
- **Identification of disease-causing variants for:**
  - **Newborn Screening**
  - **Diagnosis**
  - **Predictive testing**
  - **Carrier detection**
  - **Prenatal screening**
  - **Preimplantation testing**
  - **Pharmacogenetics**

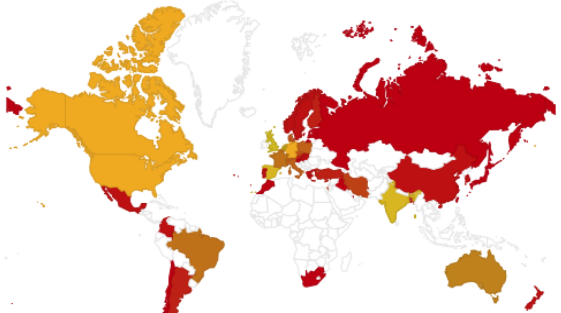
https://www.ncbi.nlm.nih.gov/gtr/

About GTR®

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

- How to use GTR ▪ Frequently asked questions ▪ GTR News
- GTR Information at NIH Office of the Director ▪ GTR in the community
- Contact us and provide feedback

Worldwide Lab Participation in GTR



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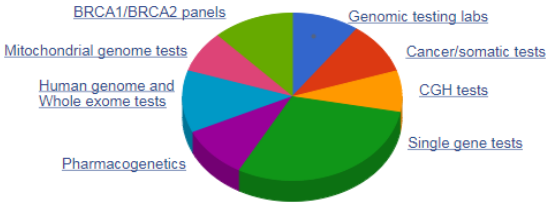
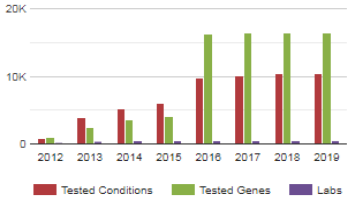
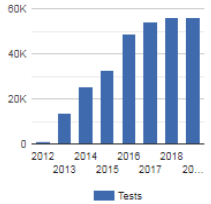


All GTR data

GTR Data





FTP: Download GTR data and documents

Locate a Genetics Professional

- ABGC Directory ▪ ABMGG Directory ▪ NSGC Directory
- NCI Cancer Genetics Services Directory ▪ ACMG Genetics Clinics Database

Resources Included in GTR

GTR includes information from resources such as ClinVar and MedGen from within the NIH and many resources from outside the NIH.

See a list of all related resources

Distinction Between Different Variants

Pathogenic Variants (mutations): Changes in the DNA, which are 'rare'; can be private; newer; disease-causing

Benign Variants (SNPs/Polymorphisms): Changes in the DNA occurring at a higher frequency, usually greater than 1%; may start as pathogenic and reach a higher frequency; older changes.

Both are inherited and can be used to track DNA changes

cSNPs are in the coding region

synonymous:	no change to the amino acid (silent)
non-synonymous:	change to the amino acid

Non-coding SNPs: promoter, splice sites, stability, other regulatory changes

Types of Pathogenic Variants

- *Normal*

CCG GGA AGC AAU
Pro Gly Ser Asn

- *Missense*

CCG GCA AGC AAU
Pro Val Ser Asn

- *Nonsense*

CCG UGA AGC AAU
Pro STOP

- *Frameshift (insertion)*

CCG AGG AAG CAA
Pro Arg Lys Gln

- *Frameshift (deletion)*

CCG GAA GCA AUG
Pro Glu Asp Met

- *Trinucleotide*

CAG CAG CAG CAG
Gln Gln Gln Gln

History of Molecular Testing in Newborn Screening

1994

-- Washington – hemoglobin confirmatory testing (Hb S, C, E by RFLP)

-- Wisconsin – CFTR testing for ΔF508

1998

-- New England – p.Q188R & p.N314D in GALT by RFLP

1999

-- New England – MCADD (c.985A>G) by RFLP

History of Molecular Testing in Newborn Screening

2005 -- Wisconsin – MSUD (p.Y438N)

2006 -- New York – Krabbe disease (full gene DNA sequence analysis); ALD (2013); Pompe (2014); CFTR (NGS) (2017); SMA; MPSI and GAMT deficiency (2018)

2008 -- Wisconsin – SCID – TREC analysis

1st use of molecular test as a primary full population screen

2017 -- 42 NBSPs in US do CF molecular testing

2018 – All 50 states screen for SCID; SMA added to RUSP

Uses of Molecular Tests in NBS

Primary Screening Test

- TREC analysis for detection of SCID; SMA (18 states)

Second-Tier Test

- DNA test results provide supplemental information to assist with diagnosis
  - Often provided in separate report
  - β-globin and GALT gene analysis
- Genotypic information is required for interpretation of the screen result
  - Cystic fibrosis gene analysis

NBS Molecular Tests in US

- **Primary screen – SCID; SMA pilot**
- **Second-tier screen**
  - -- **Hemoglobinopathies**
  - -- **Galactosemia**
  - -- **Cystic fibrosis** *(targeted panel; NGS)*
  - -- **MCAD and other FAOs (VLCAD?)**
  - -- **Phenylketonuria**
  - -- **Krabbe disease; Pompe disease; GAMT; MPSI**
  - -- **Maple syrup urine disease** *(population-specific)*
  - -- **Adrenoleukodystrophy (FYI)**

Things for Programs to Consider

- Which tests will have a molecular component?
- DNA extraction methods; (cost/labor)
- Degree of automation; vendors and contracts
- Manipulation (single tube? 96-well? 384-well?)
- # Instruments, data collection, interpretation
- Staff training (lab and follow-up)

Testing by Contract -- Consider

- Specimen transport
- Screening or confirmatory?
- Timing and prioritization for contract lab
- NBS turnaround time (quality indicators)
- Systems integration
- Follow-up integration

Things for Programs to Consider In-House 1

- Volume / quality of specimens
- Cost ($$$) per sample
- “Simple test” mentality
- Public health infrastructure
  - -- Equipment
  - -- Space
- ELSI
- Have test, no Tx

See Molecular Resources page

Things for Programs to Consider In-House 2

- Capacity – Throughput -- Automation?
- IVD v. ASR / LDT and FDA implications;
- Expertise / Interpretation
- Methods / Manipulation – single tube? 96-well or 384-well plates
- Control Materials; Proficiency Testing
- Integration into Program / LIMs / Follow-up / TAT

Potential Future Applications of Molecular Testing in NBS

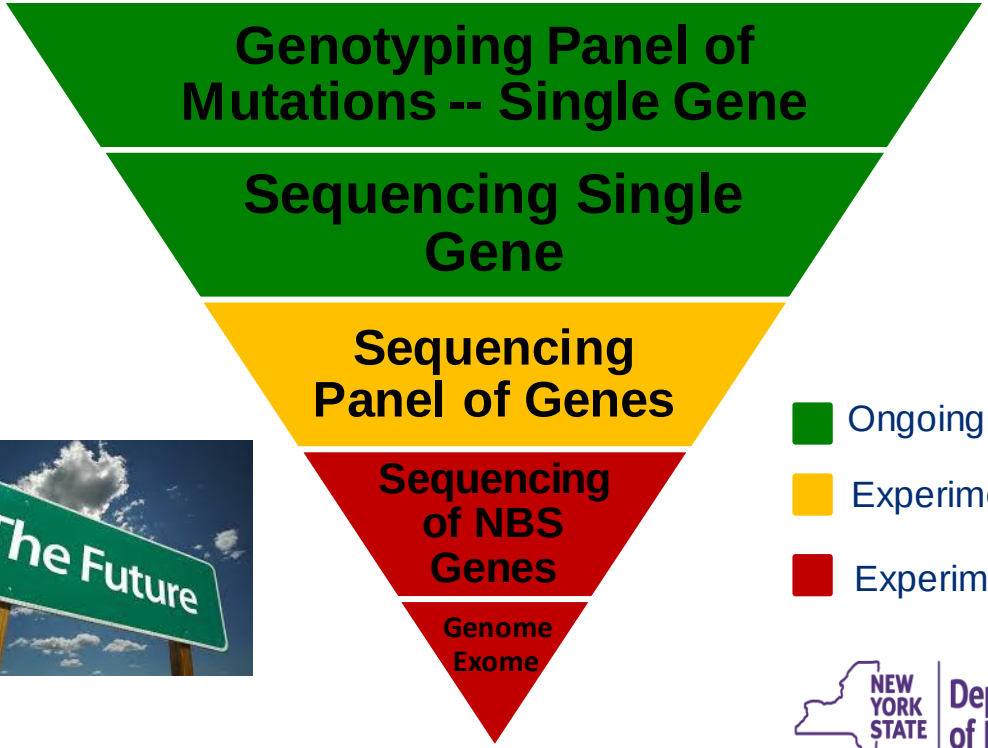
Expansion to existing or potential NBS disorders

- Congenital adrenal hyperplasia (CAH)
- Biotinidase deficiency
- Ornithine transcarbamylase deficiency (OTC)
- Cytomegalovirus and other infectious agents
- Fragile X syndrome
- Duchenne muscular dystrophy (DMD)
- Other lysosomal storage disorders (LSD)
- Cerebrotendinous xanthomatosis
- Menkes disease

Personalized Medicine in NBS

- ORKAMBI (lumacaftor/ivacaftor; p.508del/p.508del); $$$
- KALYDECO (ivacaftor; conductance variants); $$$
- Ataluren (TRANSLARNA; formerly PTC124) orphan drug exemption; CF and DMD; reads through nonsense or STOP mutations; $$$
- SPINRAZA (nusinersen) – enhances SMN2 full length transcript production; intrathecal; anti-sense oligonucleotide; $$$
- Zolgensma gene therapy for SMA – gene replacement
- Oxbryta (voxelotor) – blocks HbSS polymerization
- CRISPR – sickle cell disease; others?

Molecular Analysis in Newborn Screening
A Staged Approach



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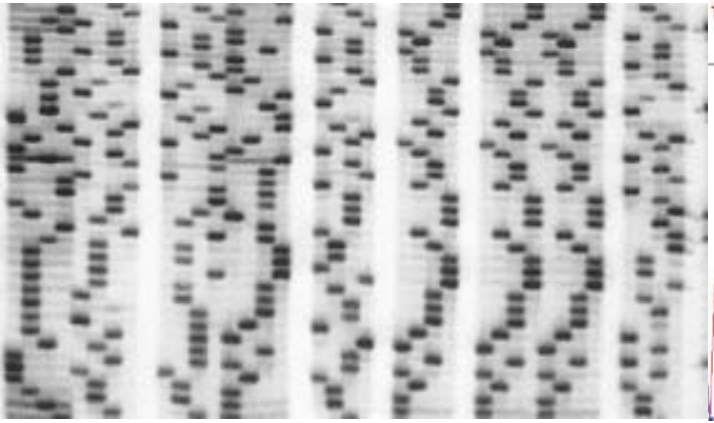
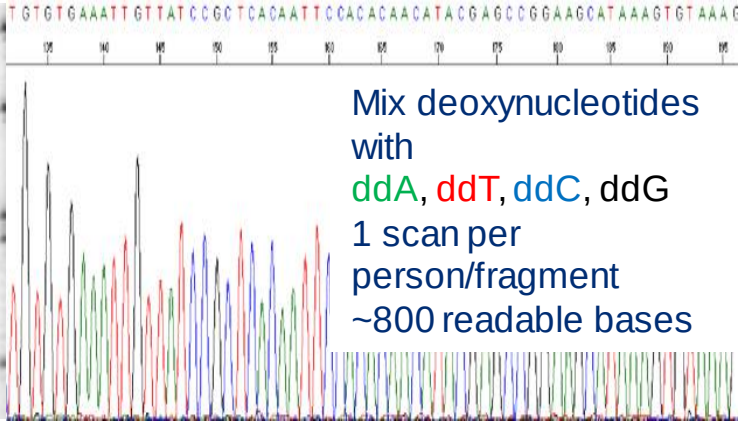
S. Cordovado, Ph.D.





Mix deoxynucleotides with
ddA, ddT, ddC, ddG
1 scan per person/fragment
~800 readable bases

Mix deoxynucleotides with
ddA, ddT, ddC*, ddG
4 lanes per person/fragment
~200 readable bases

- **Chop up the human genome**
- **Make a library of fragments**
- **Sequence billions of bases**
- **Multiplexing multiple people**
- **Millions of ‘reads’**

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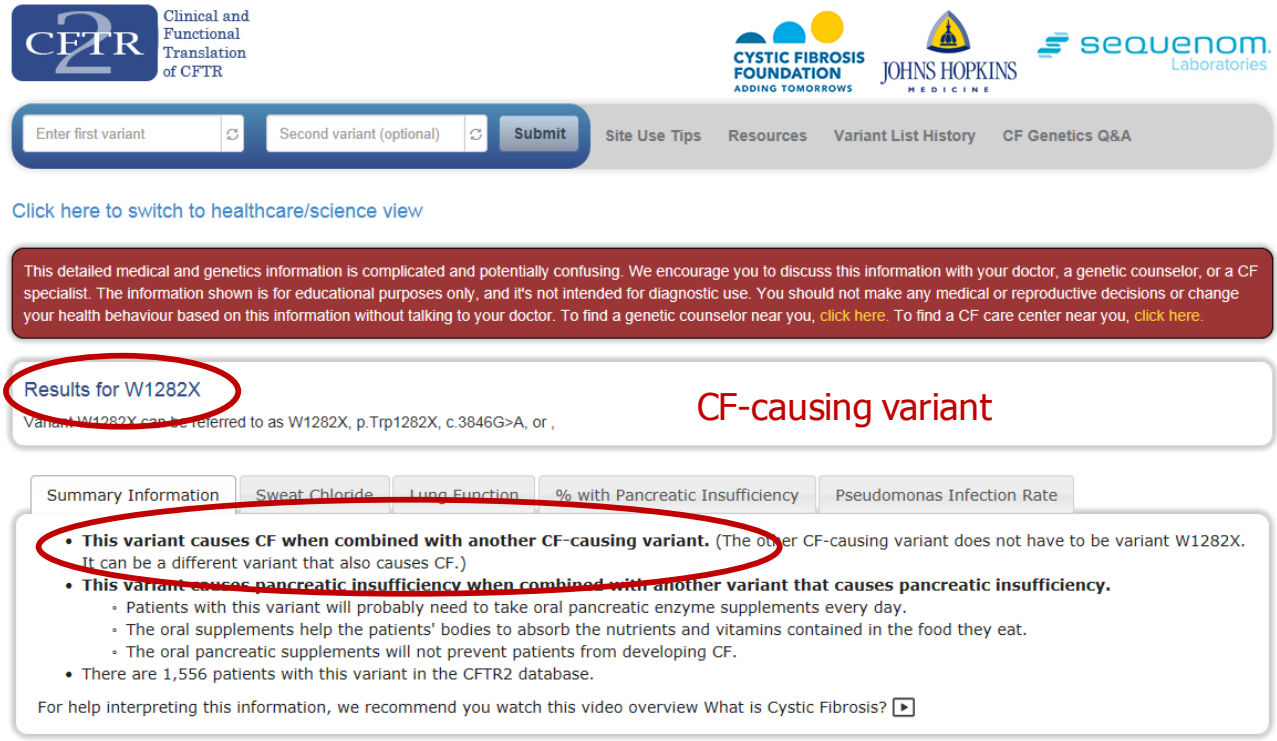
There are several products on the market that offer testing for 150, 190, and even more conditions

Q: Is that always "best for baby"? Sometimes less is more!

Challenges of Sequencing

- **Major Challenge: Determining pathogenicity**
- **ACMG defined 5 categories to classify variants:**
  - **Known pathogenic**
  - **Likely to be pathogenic**
  - **Unknown significance**
  - **Likely to be benign**
  - **Benign**

- **Knowledge accruing daily, however the medical impact of most variants is unknown**



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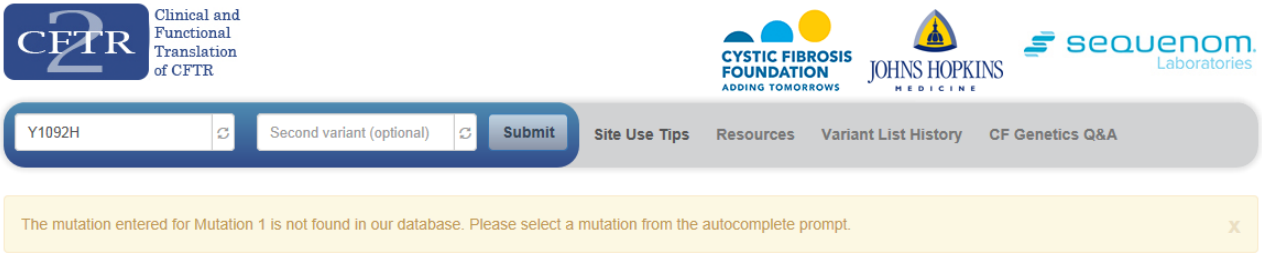
CFTR2 Clinical and Functional Translation of CFTR
CYSTIC FIBROSIS FOUNDATION ADDING TOMORROWS
JOHNS HOPKINS MEDICINE
sequenom Laboratories
Enter first variant
Second variant (optional)
Submit
Site Use Tips
Resources
Variant List History
CF Genetics Q&A
Click here to switch to healthcare/science view
This detailed medical and genetics information is complicated and potentially confusing. We encourage you to discuss this information with your doctor, a genetic counselor, or a CF specialist. The information shown is for educational purposes only, and it's not intended for diagnostic use. You should not make any medical or reproductive decisions or change your health behaviour based on this information without talking to your doctor. To find a genetic counselor near you, click here. To find a CF care center near you, click here.
Results for D1152H
Variant of Varying Clinical Consequence
• The drug ivacaftor (Kalydeco) has been approved in some countries for individuals with this variant. Please contact your physician to discuss whether ivacaftor (Kalydeco) is appropriate for you.
Summary Information
Sweat Chloride
Lung Function
% with Pancreatic Insufficiency
Pseudomonas Infection Rate
• This variant has varying consequences.
• Some patients with this variant, combined with another CF-causing variant, have CF.
• Other patients with this variant, combined with another CF causing variant, do not have CF.
• Because of this variability, it is very important that CLINICAL CRITERIA ALONE be used to determine whether a person with this variant has CF.
• Because the clinical manifestations of CF can vary over the course of a person's lifetime, people who have this variant plus a variant that is known to cause CF should have periodic check-ups with their doctor even if they have no clinical signs or symptoms of CF at the present time.
• Clinical information shown below is taken only from patients in the CFTR2 database who have been diagnosed with CF.
◦ There are other people with this variant who do NOT have CF. Information from these people is NOT included in the clinical information below, because these individuals are not followed at a CF center and are not part of the CFTR2 database. Therefore, the data below is not representative of every person with this variant.
• Patients with CF who have this variant are likely to be pancreatic sufficient. This means they may not need to take oral pancreatic enzyme supplements every day.
• There are 556 patients with this variant in the CFTR2 database.
For help interpreting this information, we recommend you watch this video overview What is Cystic Fibrosis?

Identification of Variants NOT in CFTR2

Example: Y1092H



Classification of Variants NOT in CFTR2

ACMG STANDARDS AND GUIDELINES | Genetics inMedicine

Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology

Sue Richards, PhD[1], Nazneen Aziz, PhD[2,16], Sherri Bale, PhD[3], David Bick, MD[4], Soma Das, PhD[5], Julie Gastier-Foster, PhD[6,7,8], Wayne W. Grody, MD, PhD[9,10,11], Madhuri Hegde, PhD[12], Elaine Lyon, PhD[13], Elaine Spector, PhD[14], Karl Voelkerding, MD[13] and Heidi L. Rehm, PhD[15]; on behalf of the ACMG Laboratory Quality Assurance Committee

Genet Med. 2015 May;17(5):405-24

Perils of Newborn Screening: Scientific American - Windows Internet Explorer

http://www.scientificamerican.com/article.cfm?id=perils-of-newborn-screening

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Perils of Newborn Screening

Doctors may be testing infants for too many diseases

By Ariel Bleicher

The first symptoms often appear a month or two after birth. The babies' muscles stiffen. They lose their hearing and vision, stop sleeping and scream in pain. Some develop seizures. By the time many parents learn that their children have Krabbe disease—a rare genetic disorder that degrades nerve cells—it is too late for the only viable treatment, a transfusion of umbilical cord blood stem cells from healthy donors.

RESIDUAL SPECIMEN STORAGE

ClinVar

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Advanced Help

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ClinVar

ClinVar aggregates information about genomic variation and its relationship to human health.

Using ClinVar

- About ClinVar
- Data Dictionary
- Downloads/FTP site
- FAQ
- Contact Us
- RSS feed/What's new?
- Factsheet

Tools

- ACMG Recommendations for Reporting of Incidental Findings
- ClinVar Submission Portal
- Submissions
- Variation Viewer
- Clinical Remapping - Between assemblies and RefSeqGenes
- RefSeqGene/LRG

Related Sites

- ClinGen
- GeneReviews ®
- GTR ®
- MedGen
- OMIM ®
- Variation

Submitter highlights

We gratefully acknowledge those who have submitted data and provided advice during the development of ClinVar.

Follow us on Twitter to receive announcements of the release of new datasets.

Want to learn more about who submits to ClinVar?

- Read information about groups that submit to ClinVar
- See the list of submitters with the number of records each has submitted
- View a world map of ClinVar submitters

Disclaimer

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely

Elements Console Sources Network Performance Memory Application Security Audits 1 7

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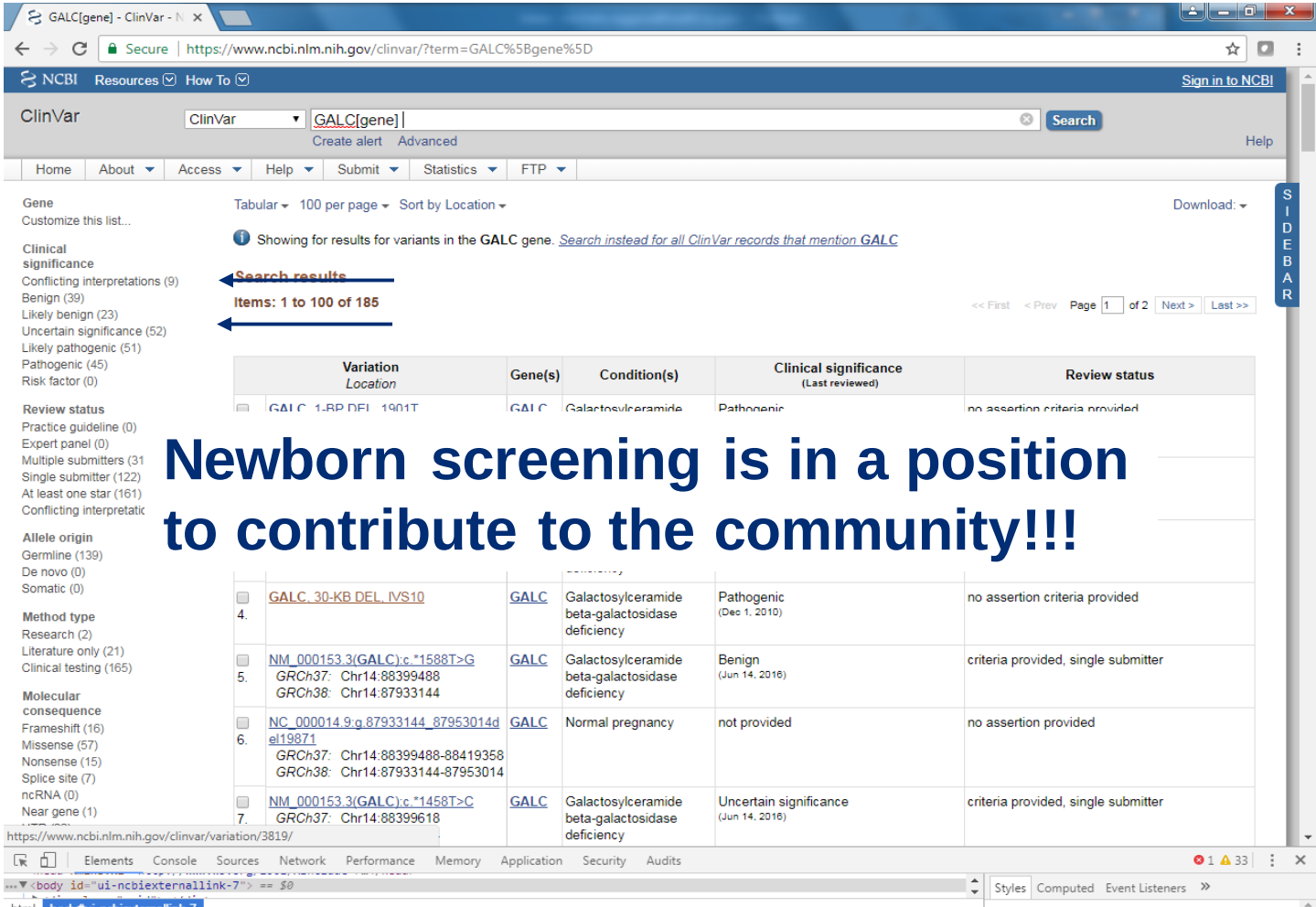
Styles Computed Event Listeners

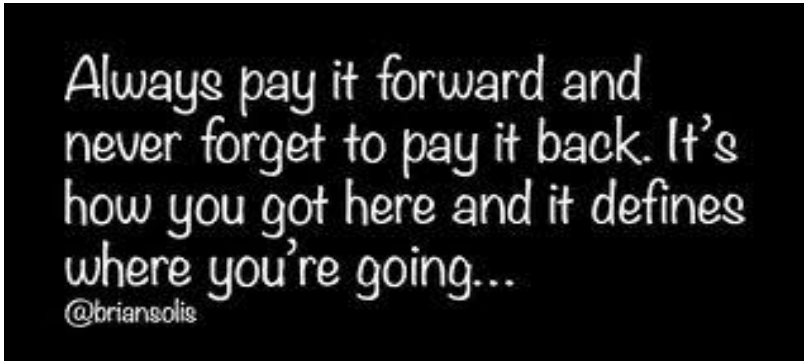

GALC[gene] - ClinVar
Secure https://www.ncbi.nlm.nih.gov/clinvar/?term=GALC%5Bgene%5D
NCBI Resources How To Sign in to NCBI
ClinVar
ClinVar GALC[gene] Search
Create alert Advanced Help
Home About Access Help Submit Statistics FTP
Gene
Customize this list...
Clinical significance
Conflicting interpretations (9)
Benign (39)
Likely benign (23)
Uncertain significance (52)
Likely pathogenic (51)
Pathogenic (45)
Risk factor (0)
Review status
Practice guideline (0)
Expert panel (0)
Multiple submitters (31
Single submitter (122)
At least one star (161)
Conflicting interpretatic
Allele origin
Germline (139)
De novo (0)
Somatic (0)
Method type
Research (2)
Literature only (21)
Clinical testing (165)
Molecular consequence
Frameshift (16)
Missense (57)
Nonsense (15)
Splice site (7)
ncRNA (0)
Near gene (1)
Tabular 100 per page Sort by Location Download:
Showing for results for variants in the GALC gene. Search instead for all ClinVar records that mention GALC
Search results
Items: 1 to 100 of 185
<< First < Prev Page 1 of 2 Next > Last >>
SIDEBAR
Variation Location
Gene(s)
Condition(s)
Clinical significance (Last reviewed)
Review status
GALC, 30-KB DEL, IVS10
GALC
Galactosylceramide beta-galactosidase deficiency
Pathogenic (Dec 1, 2010)
no assertion criteria provided
NM_000153.3(GALC):c.*1588T>G
GRCh37: Chr14:88399488
GRCh38: Chr14:87933144
GALC
Galactosylceramide beta-galactosidase deficiency
Benign (Jun 14, 2016)
criteria provided, single submitter
NC_000014.9:g.87933144_87953014del19871
GRCh37: Chr14:88399488-88419358
GRCh38: Chr14:87933144-87953014
GALC
Normal pregnancy
not provided
no assertion provided
NM_000153.3(GALC):c.*1458T>C
GRCh37: Chr14:88399618
GALC
Galactosylceramide beta-galactosidase deficiency
Uncertain significance (Jun 14, 2016)
criteria provided, single submitter
Newborn screening is in a position to contribute to the community!!!
https://www.ncbi.nlm.nih.gov/clinvar/variation/3819/
Elements Console Sources Network Performance Memory Application Security Audits
Styles Computed Event Listeners

Improvement of the Literature

http://www.miragebookmark.ch/images/astronomy-library-utrecht.jpg

Learning Points

- Newborn screening has accepted new technology and evolved over time
- Molecular NBS began in 1994 and continues to include more testing; complexity is increasing
- Almost all NBS invokes genetics and thus the family
- Programs need to address utility and laboratory needs for molecular NBS
- Molecular testing will continue to enter NBS algorithms and sequencing poses challenges for programs to consider



Thanks to Suzanne Cordovado, Ph.D. Susan Tanksley, Ph.D., Denise Kay, Ph.D. and Rachel Lee, Ph.D. for slides