The Future of Newborn Screening Technology: Looking Ahead

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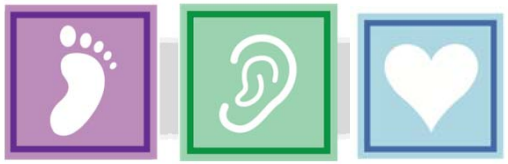
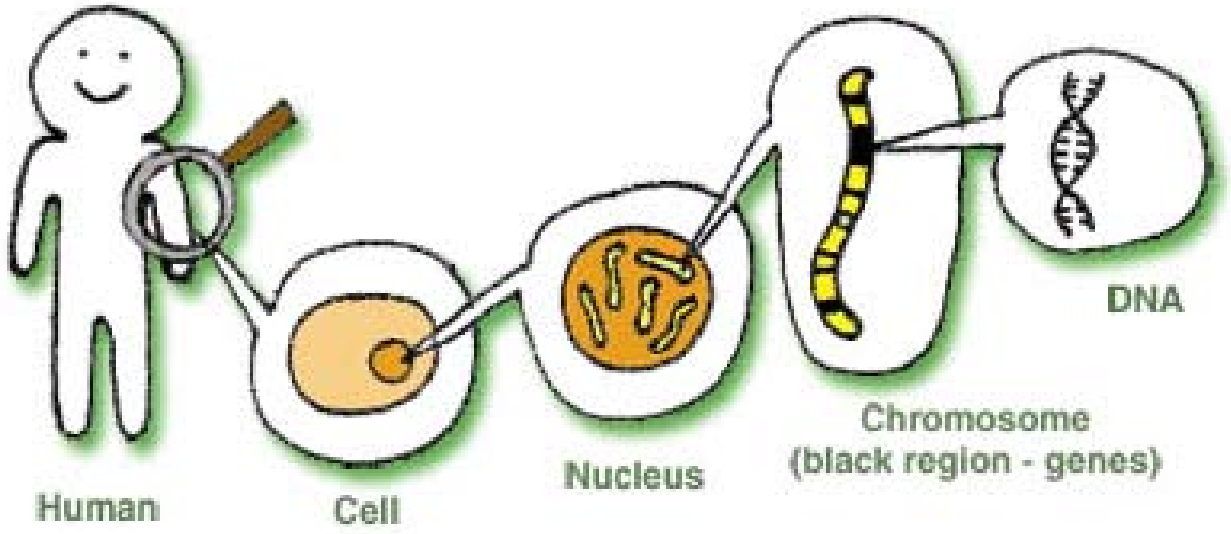
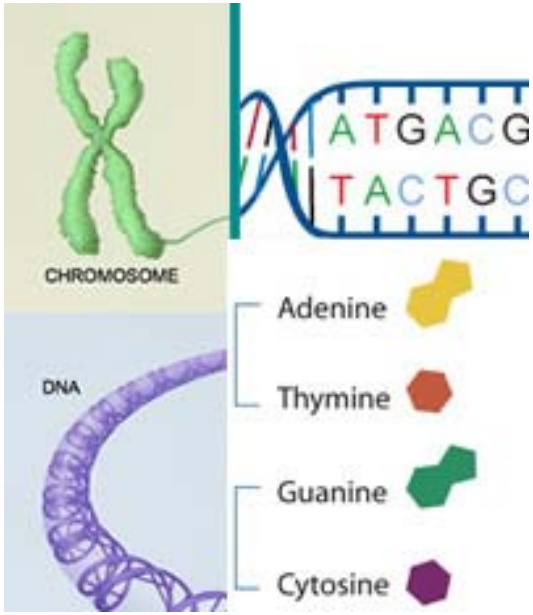


Genetics Overview



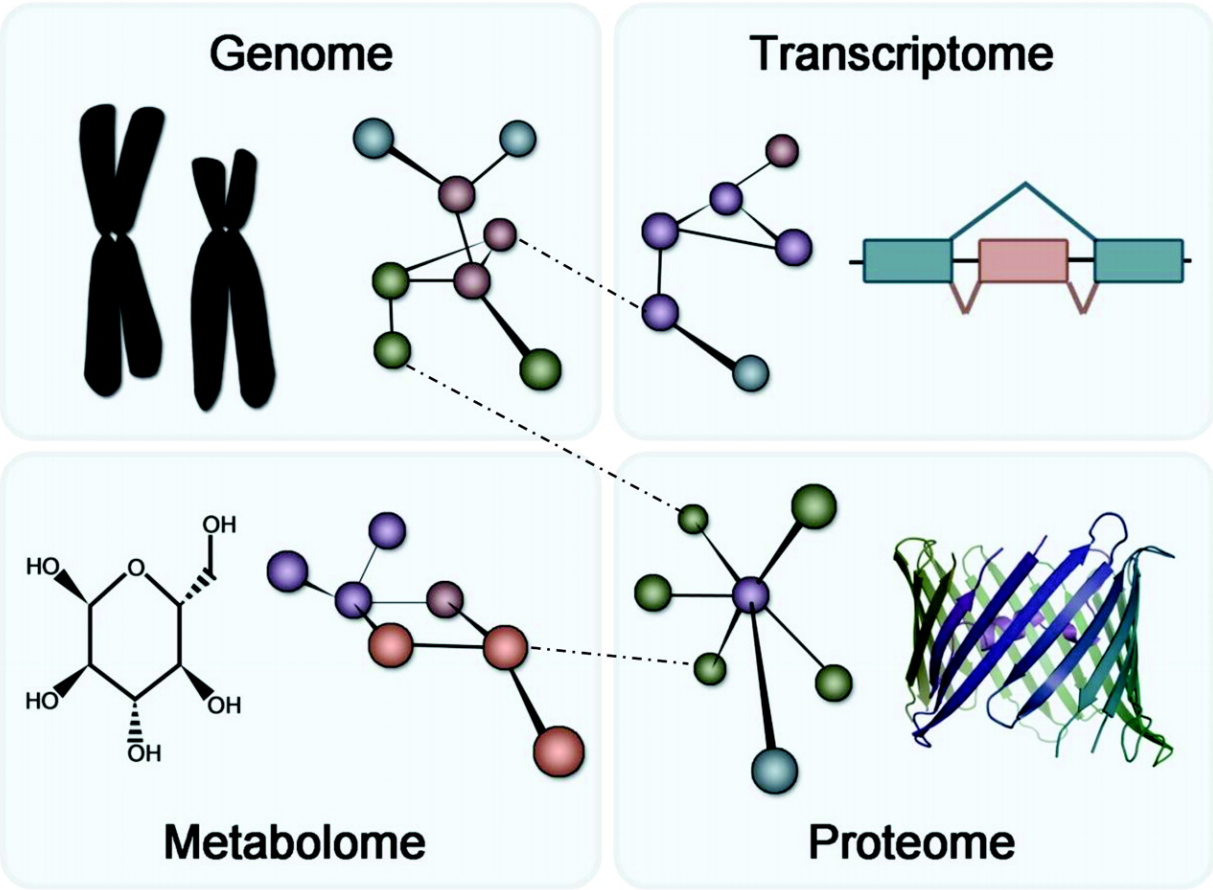
www.ashg.org



www.genome.gov

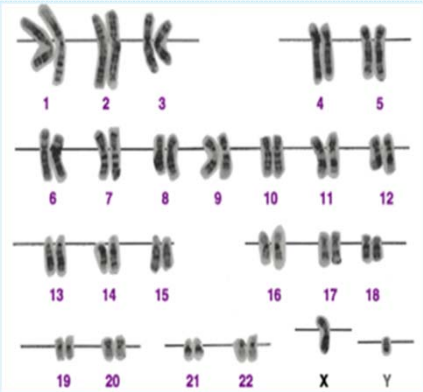
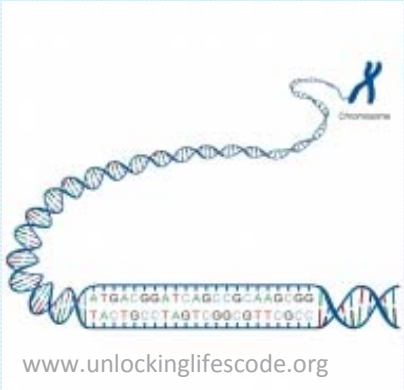
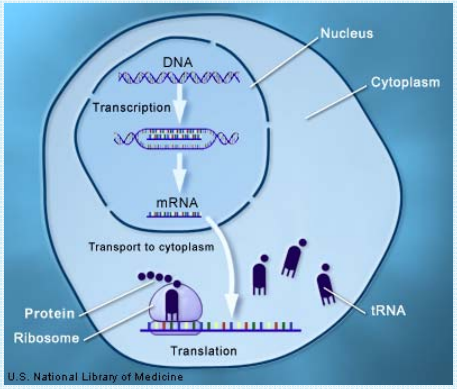
Evolution of the Central Dogma

DNA ⟶ RNA ⟶ protein



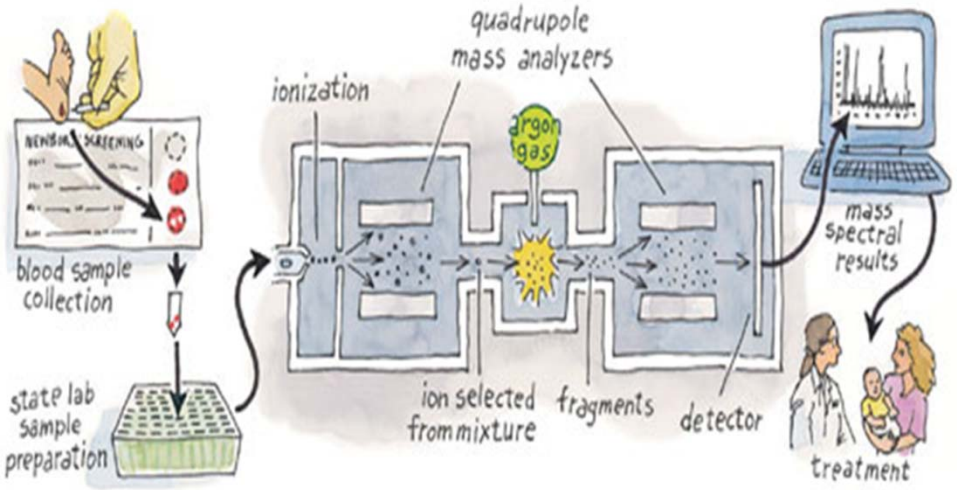
Sarah Franklin, and Thomas M. Vondriska Circ Cardiovasc Genet. 2011;4:576

Genetics Overview

Chromosomes	Genes	Proteins
46 (23 pairs)	20-25,000	~100,000
Strings of genes	Segments of DNA	Strings of amino acids
Package and help ensure DNA copied and distributed in cell division	Issue chemically coded messages to make a product (protein)	Body's work force to ensure normal development & health
		

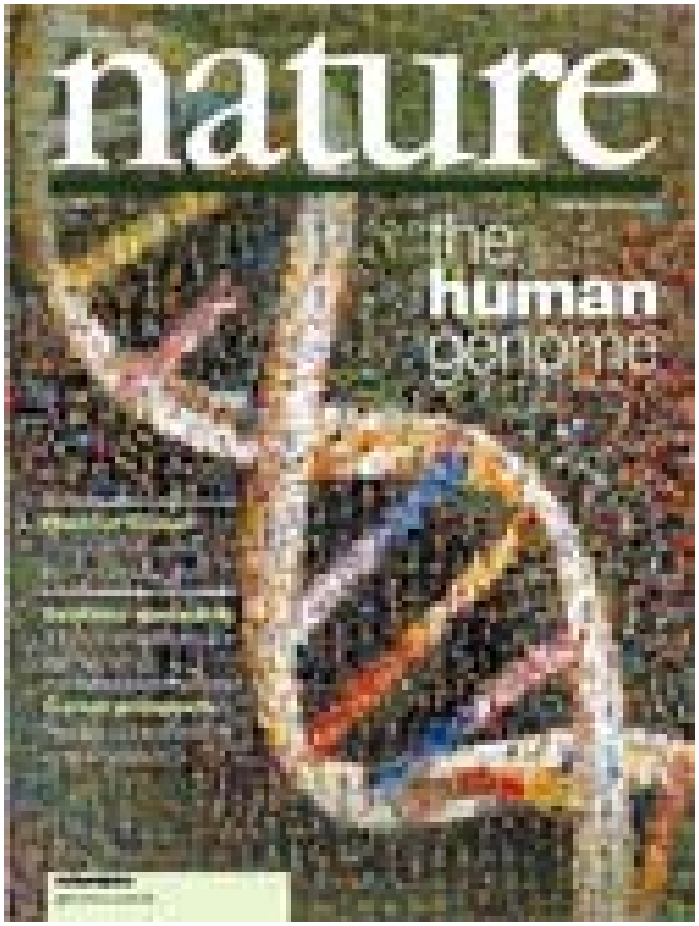
Tandem Mass Spectrometry Revolutionized NBS

- April 2014-CCHD
- October 2011-SCID
- October 2007-Cystic Fibrosis and Hearing
- April 2005-31 MS/MS Disorders*
- October 2004-HCY, CIT, ASA
- April 2003-MCAD
- July 1993-CAH
- October 1987-Biotinidase Deficiency, MSUD and Hemoglobinopathies
- Spring 1985-Galactosemia
- June 1977-CH
- August 1965-Phenylketonuria



- MS/MS allows testing ~31 disorders

The Genomic Era



Genomic Sequencing for all

Exploring Sequencing of Newborns' genomes

- 4 studies in 2012 ($5 million/year for 5 years)
  - Brigham & Women's Hospital & Boston Children's Hospital (Boston)
  - Children's Mercy Hospital (Kansas City)
  - UCSF (San Francisco)
  - University of North Carolina, Chapel Hill (Chapel Hill)
- 3 component projects:
  - Acquisition & analysis of genomic datasets
  - Clinical research that advances understanding of specific disorders
  - Research related to ethical, legal and social implications of genomic sequencing in newborns
  - Consent subjects for whole genome/exome sequencing
- Data analysis context
  - How can sequencing replicate/augment results for disorders already screened for?
  - Can sequencing provide additional information about orders not screened for?
  - What clinical information can be provided relevant to clinical care?

Newborn Sequencing Benefits and Challenges

Benefits

- Improved ability to make faster diagnoses
- Improved ability to diagnose current/other disorders
- Personalized medicine
- Anticipatory guidance

Challenges

- Variants Unknown Significance
- Incidental Findings
- Genetic Testing of Newborns
- Parent Consent
- Cost

Overcoming Sequencing Challenges

Variants of Unknown Significance

- Rare variants with unclear significance
- Potential emotional toll on patient/family
- Issues for NBS Programs
  - Reporting
  - Future reclassification of variant

Unexpected Positive Findings

- Detection of previously unsuspected condition
- Detection of adult-onset condition
- Detection of risk for malignancy or dementia

Possible Solution

- Targeted Sequencing?
  - NBS Disorder Genes
- Whole exome sequencing?
  - All Exons
  - 1% of genome
  - ~85% disease-causing mutations
- Whole genome sequencing?
  - Examine entire DNA blueprint

Newborn Genetic Sequencing

- Distinction between adults and children
  - Predictive asymptomatic testing typically not performed in children
    - Inconsistent with respecting parental decision making?
    - Sustainable in era of genomic testing?
  - ACMG: reporting incidental findings to ordering clinicians not be limited by age of person sequenced
    - No comment on NBS disorders or newborn sequencing

Key issues/Questions?

- Will sequencing offer same accuracy and speed?
- Is sequencing feasible for state laboratories?
- Are there unique data storage considerations?
- How/should results be communicated over time?

Hearing loss through DNA deletion

The Boston Globe. August 26, 2013