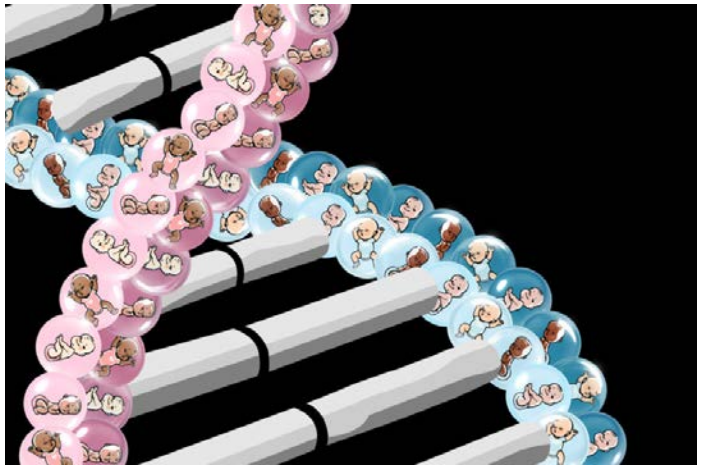


An Introduction to Genomic Sequencing in Newborn Screening: Ethical, Legal, and Social Implications

Presented to the Advisory Committee on Heritable Disorders in Newborns and Children
November 2, 2018

Cynthia M. Powell, MD

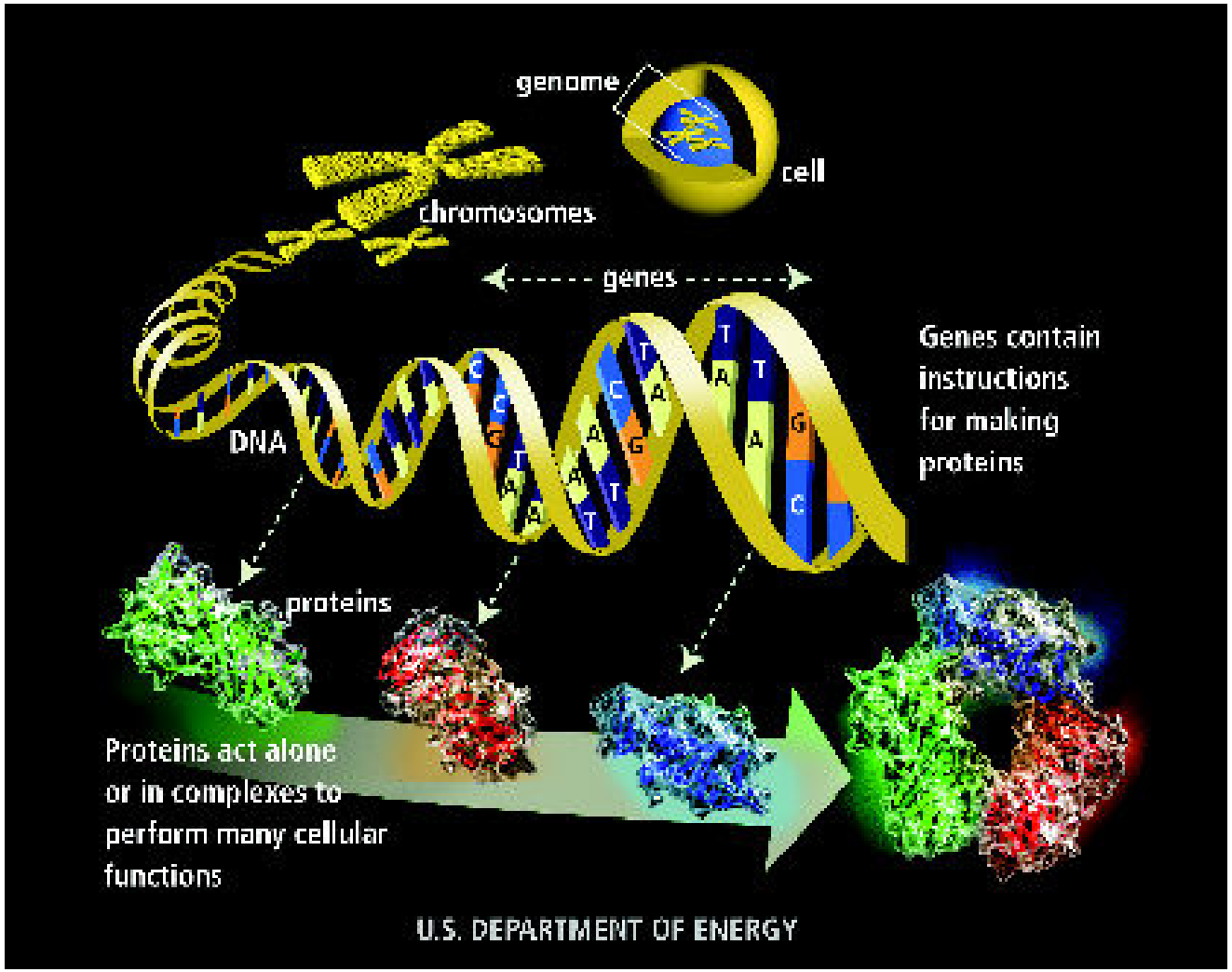
Professor of Pediatrics and Genetics

The University of North Carolina at Chapel Hill

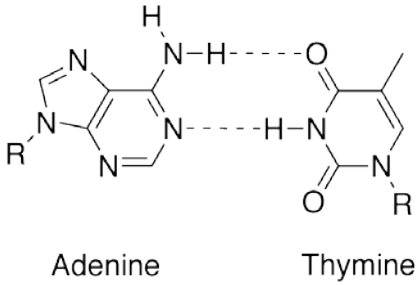
Newborn Sequencing In Genomic medicine and public HealTh (NSIGHT)

- What is genomic sequencing?
- Background of NSIGHT program
- Overview of the four NSIGHT projects
- Introduction of speakers

This research was supported by the National Institutes of health Eunice Kennedy Shriver National Institute of Child Health & Human Development and the National Human Genome Research Institute under awards: U19HD077627; U19HD077632; U19HD07767; U19HD077693.

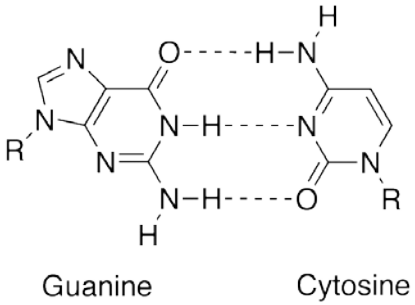

genome
cell
chromosomes
genes
DNA
Genes contain instructions for making proteins
proteins
Proteins act alone or in complexes to perform many cellular functions
U.S. DEPARTMENT OF ENERGY

DNA is made up of molecules called nucleotides

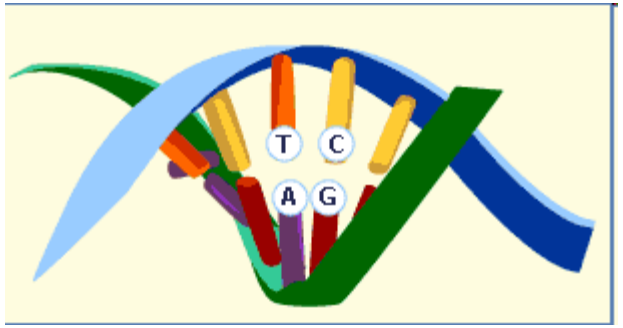


A: Adenine
T: Thymine

C: Cytosine
G: Guanine



Each nucleotide has a corresponding partner making up a “base pair”



GENE

Made up of thousands of nucleotides (base pairs)

ATGCCCTTTAGGTTACCTTTAGCCCTTAGCCCATCGGGTTACCCTTCCCCCTTACGGGCTCTT
TTATATATCCGGGCGCGCGTTAAAATATACCCATTTATATCGGACGTTTACTACCTACGGATAC
TGGGCTAGGATACTAGACTTAAACGATTAATCGGCCCTTACGCAGGTTACTACTTAGCAGTT
AATCGGGCGTTATACGGCCTAC…….

Range in size from 250 base pairs to 2,500,000 base pairs

GENE

ATGCCCTTTAGGTTACCTTTAGCCCTTAGCCCATCGGGTTACCCTTCCCCCTTACGGGCTCTT
TTATATATCCGGGCGCGCGTTAAAATATACCCATTTATATCGGACGTTTACTACCTACGGATAC
TGGGCTAGGATACTAGACTTAAACGATTAATCGGCCCTTACGCAGGTTACTACTTAGCAGTT
AATCGGGCGTTATACGGCCTAC……

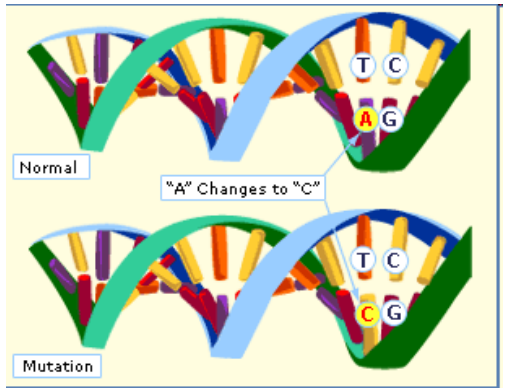
GENE VARIANT

Pathogenic “mutation” or Benign?

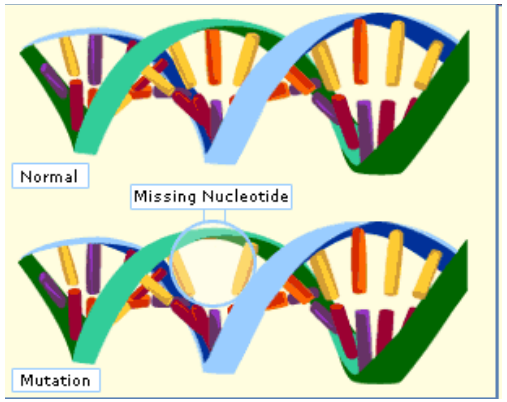
ATGCCCTTTAGGTTACCTTTAGCCCTTAGCTCATCGGGTTACCCTTCCCCCTTACGGGCTCTTT
TATATATCCGGGCGCGCGTTAAAATATACCCATTTATATCGGACGTTTACTACCTACGGATACT
GGGCTAGGATACTAGACTTAAACGATTAATCGGCCCTTACGCAGGTTACTACTTAGCAGTTA
ATCGGGCGTTATACGGCCTAC…

TYPES OF VARIANTS

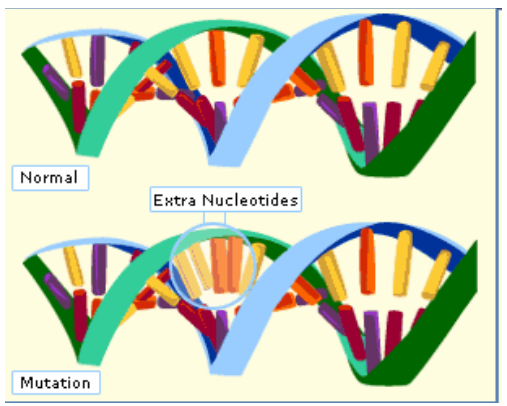
POINT



DELETION



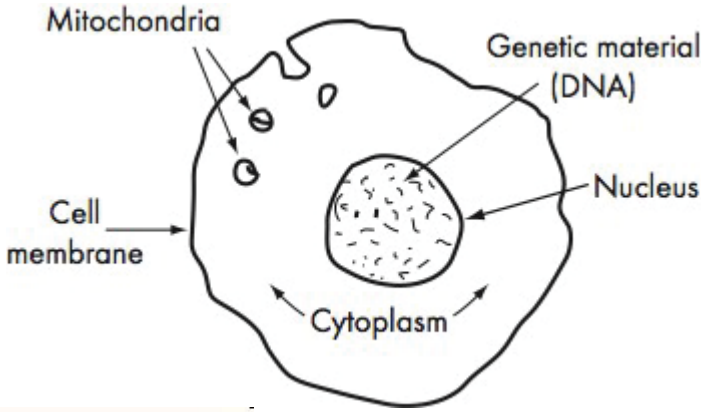
INSERTION

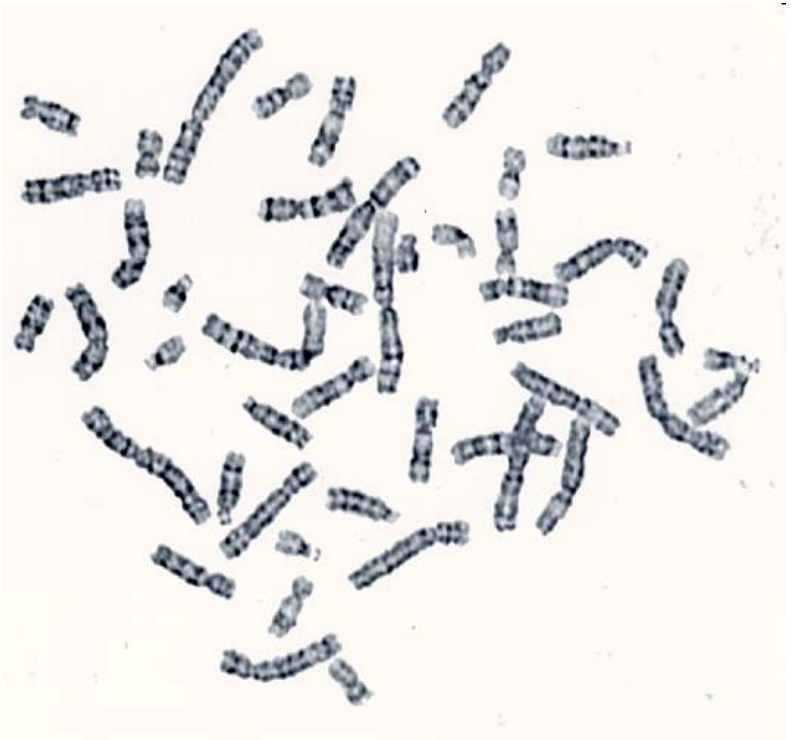


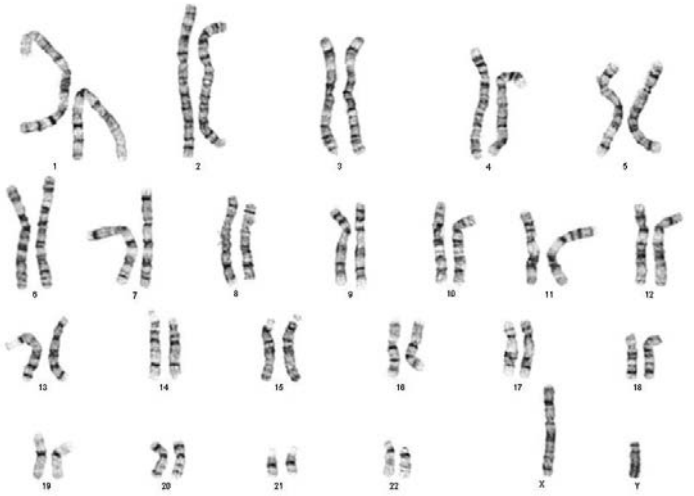
TYPES OF VARIANTS

NORMAL:	THE CAT SAW THE DOG
POINT:	THE BAT SAW THE DOG
DELETION:	THE CAT THE DOG
INSERTION:	THE CART SAW THE DOG
TRIPLET EXPANSION:	THE CAT SAW SAW SAW SAW THE DOG

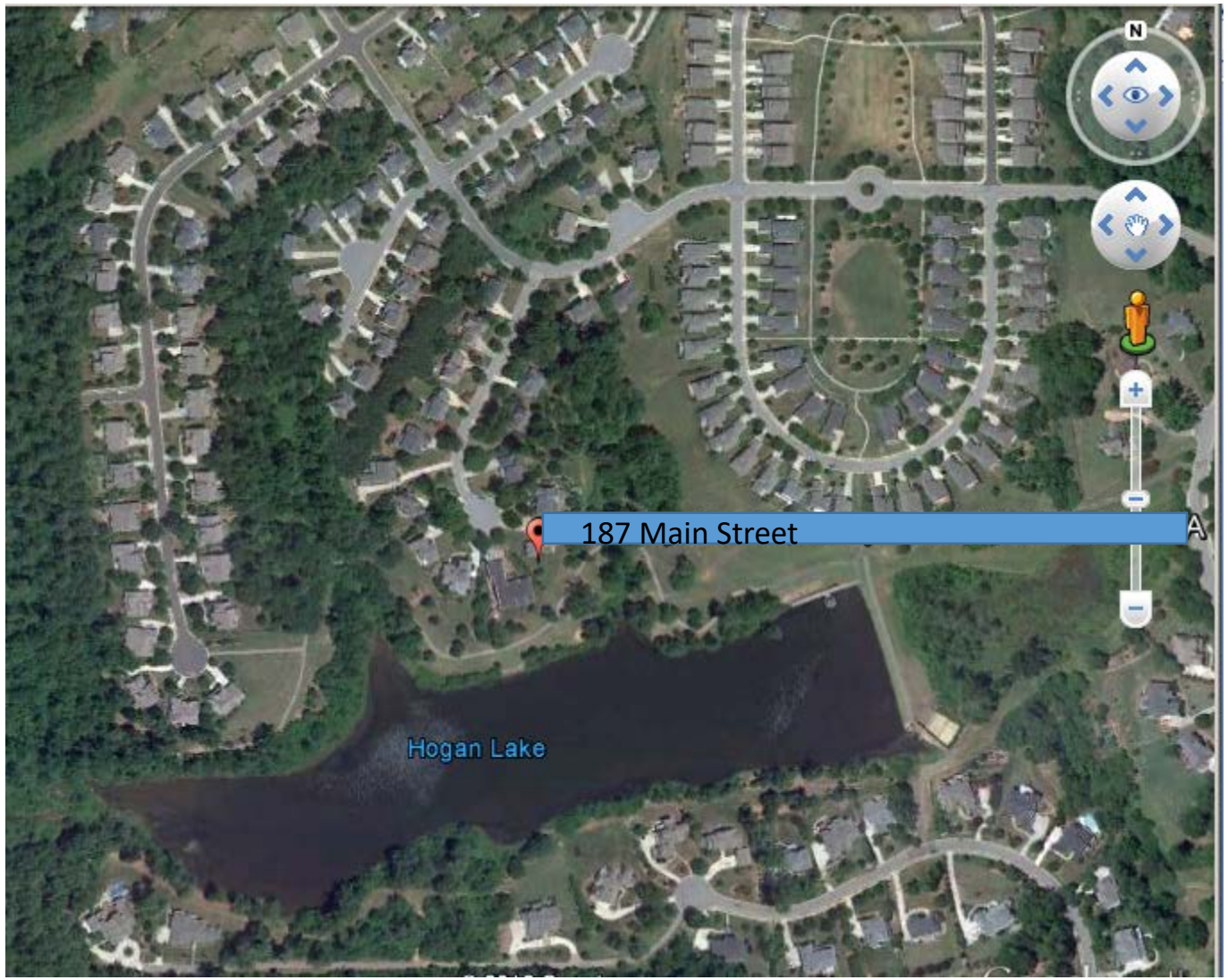
How can we look at the genome?



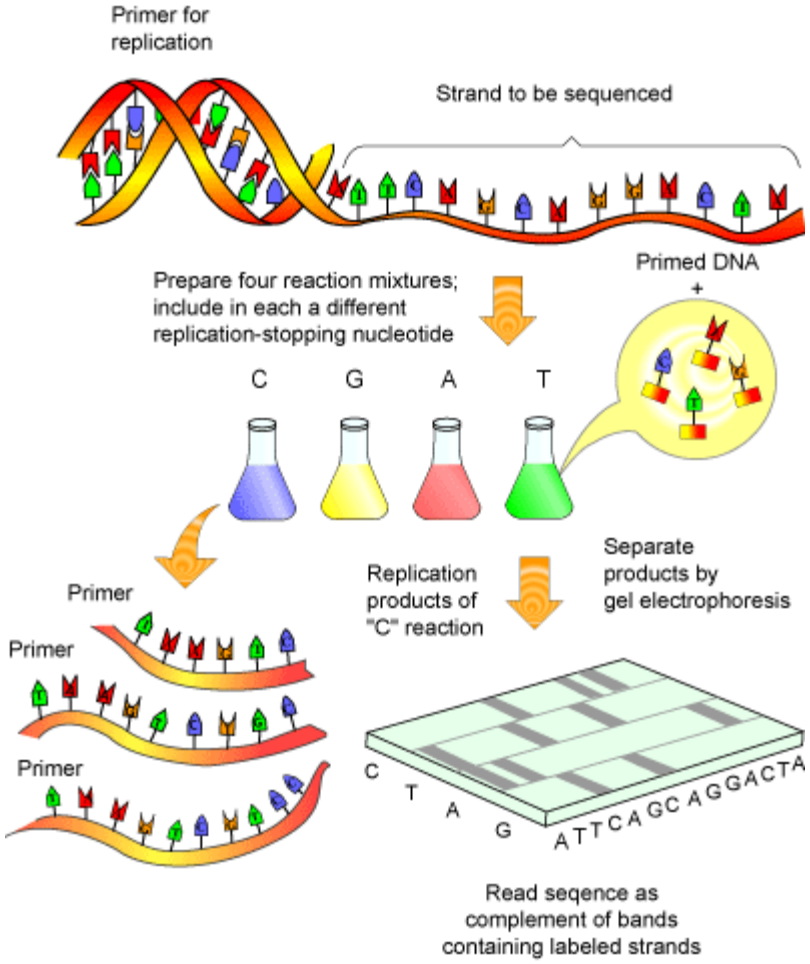




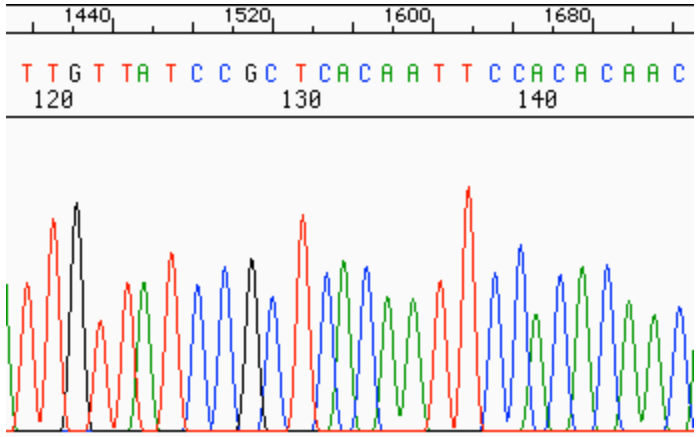
Each chromosome contains from 50 – 250 million nucleotides and from 200 – 800 protein coding genes


N
187 Main Street
A
Hogan Lake

What is sequencing?



http://www.eisenlab.org/FunFly/?page_id=24#sanger



- Each peak on chromatogram corresponds to one base pair. Typically can read 1000 bases (1 kb) per read
- This is known as Sanger sequencing after its inventor
- Also known as 1st Generation sequencing


AVERY
UPPER DEVON
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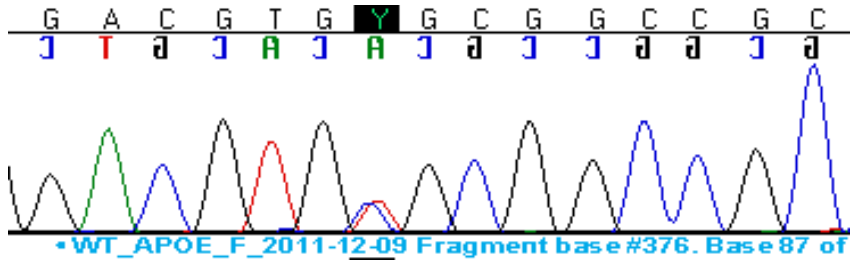
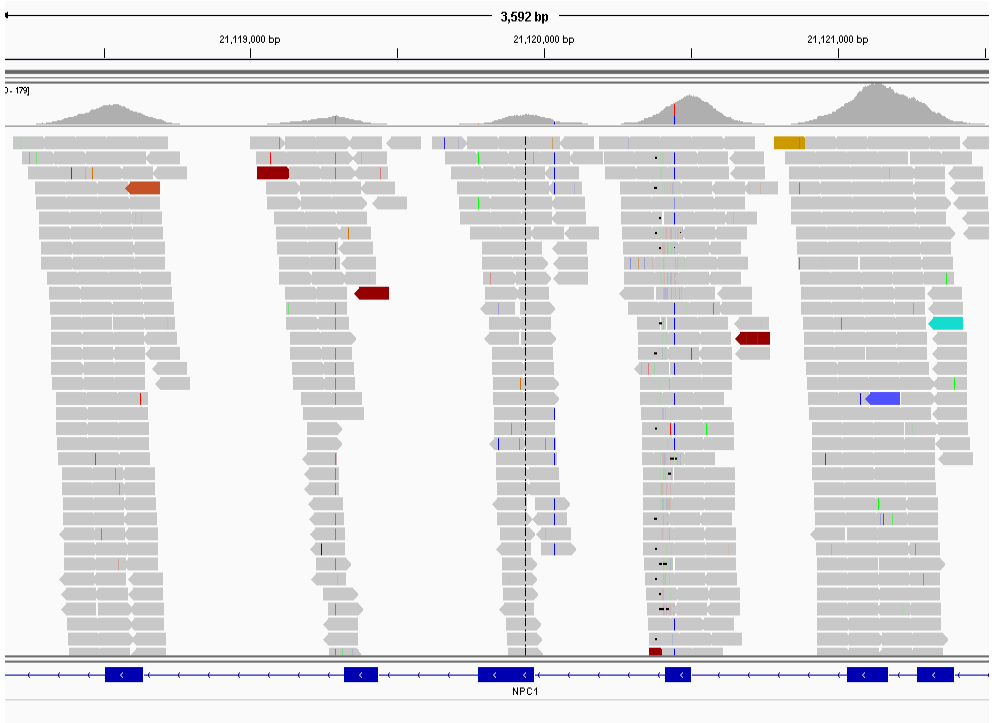
Sanger vs. Whole-Exome Sequencing: Technical Considerations

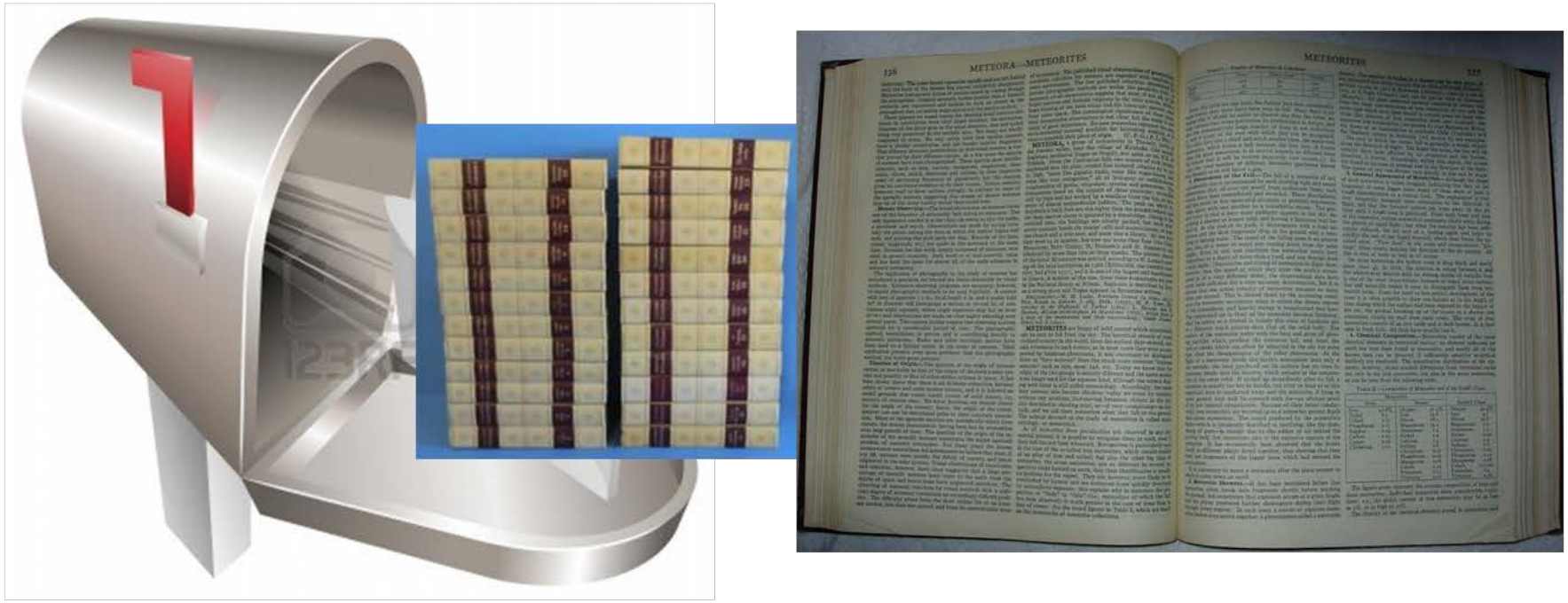
- Sanger
  - 100-800+ bp
  - Targeted mutation analysis
  - Complete coverage
  - “Gold standard”



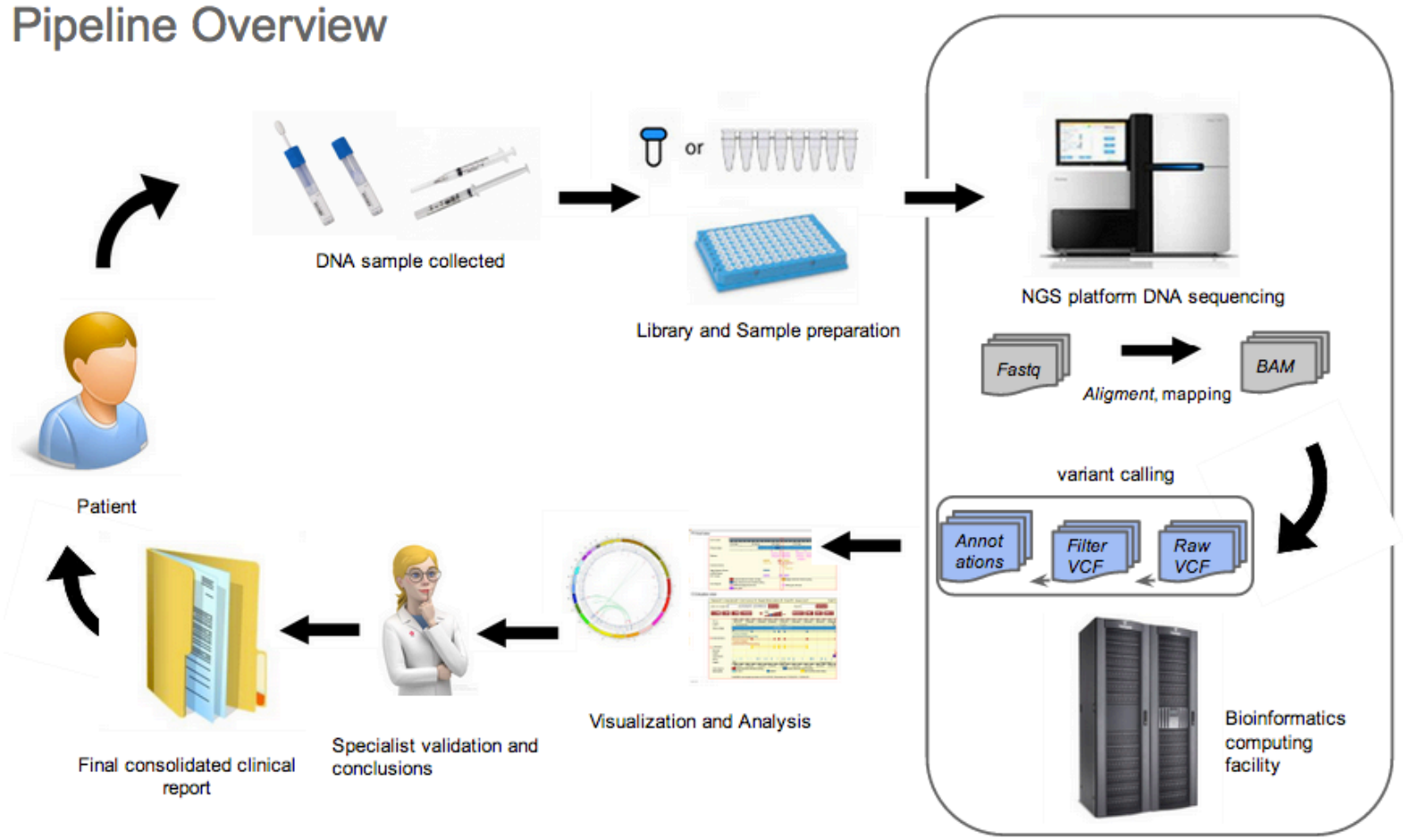
- WES
  - 30 Mb in exome (3 billion in entire genome)
  - Mutation fishing in many targets
  - Interpretation difficulties



Next Generation Sequencing



Next Generation Sequencing
(Whole Exome or Whole Genome Sequencing)



http://aimotion.blogspot.com/2014/08/mip-proposal-high-performance-pipeline-whole-exome-dna-sequencing.html

Next Gen Sequencing

- Can search for mutations in all genes (~20,000)
- Whole exome: just coding parts of genes (exons)
- Whole genome: everything (exons and introns)
- Analysis is complex – our understanding of what is a significant mutation and what is a benign polymorphism has a long way to go
- Ethical issues about what genes should be analyzed and what information should be returned to patients

Workshop Held in 2010
NICHD, NHGRI, ORDR

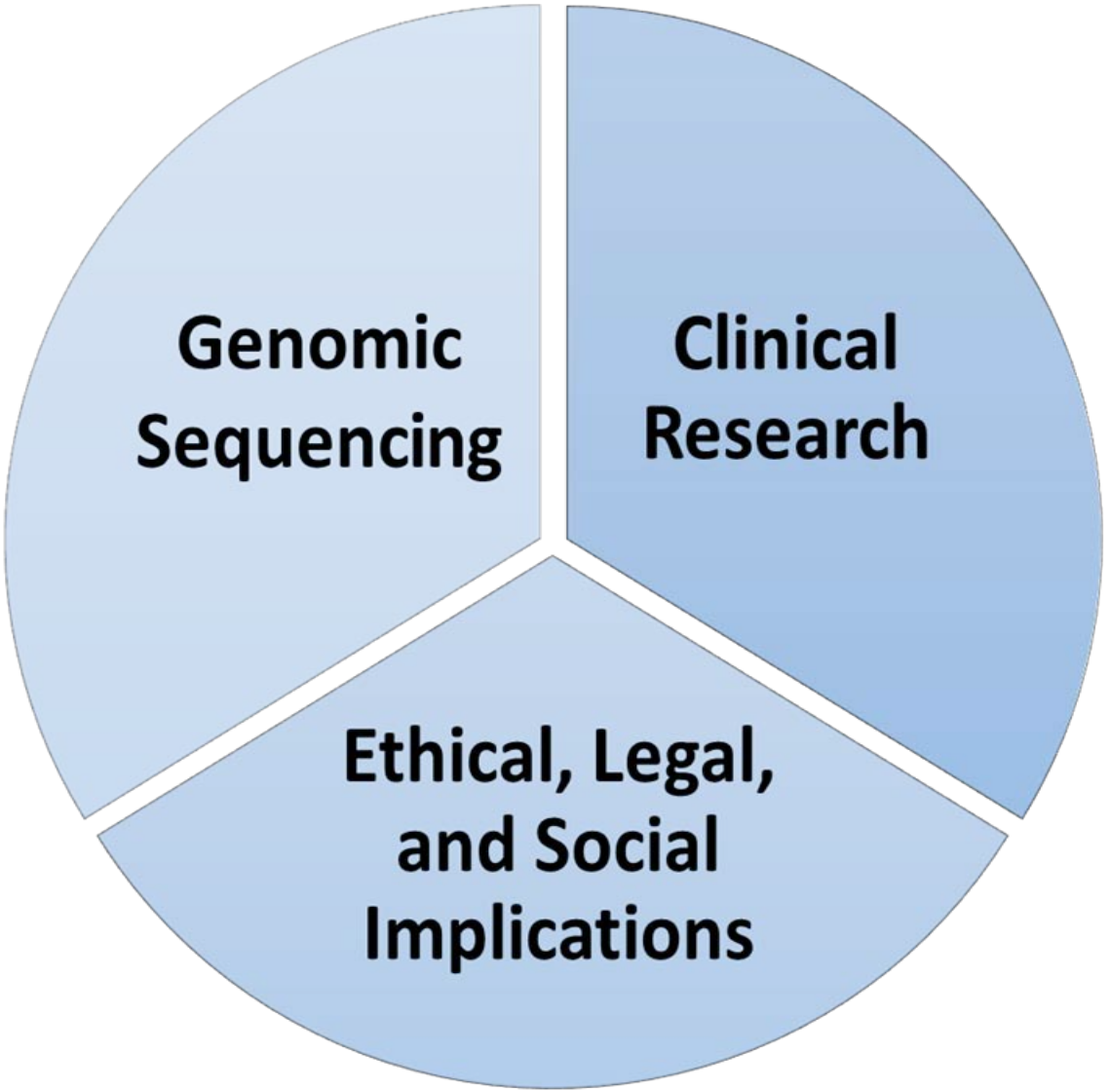
- New, sophisticated and increasingly cost-effective techniques for DNA-based sequencing and analysis may make it possible to expand newborn screening in the future and substantially expand its clinical and public health value.
- To identify elements of a trans-NIH research agenda that could inform the possible application of new genomic concepts and technologies to newborn screening and child health.
- https://www.genome.gov/pages/policyethics/staffarticles/newborn_screening_meeting_summary.pdf

U-19 RFA NIH: Genomic Sequencing and Newborn Screening Disorders NHGRI and NICHD

August 2012

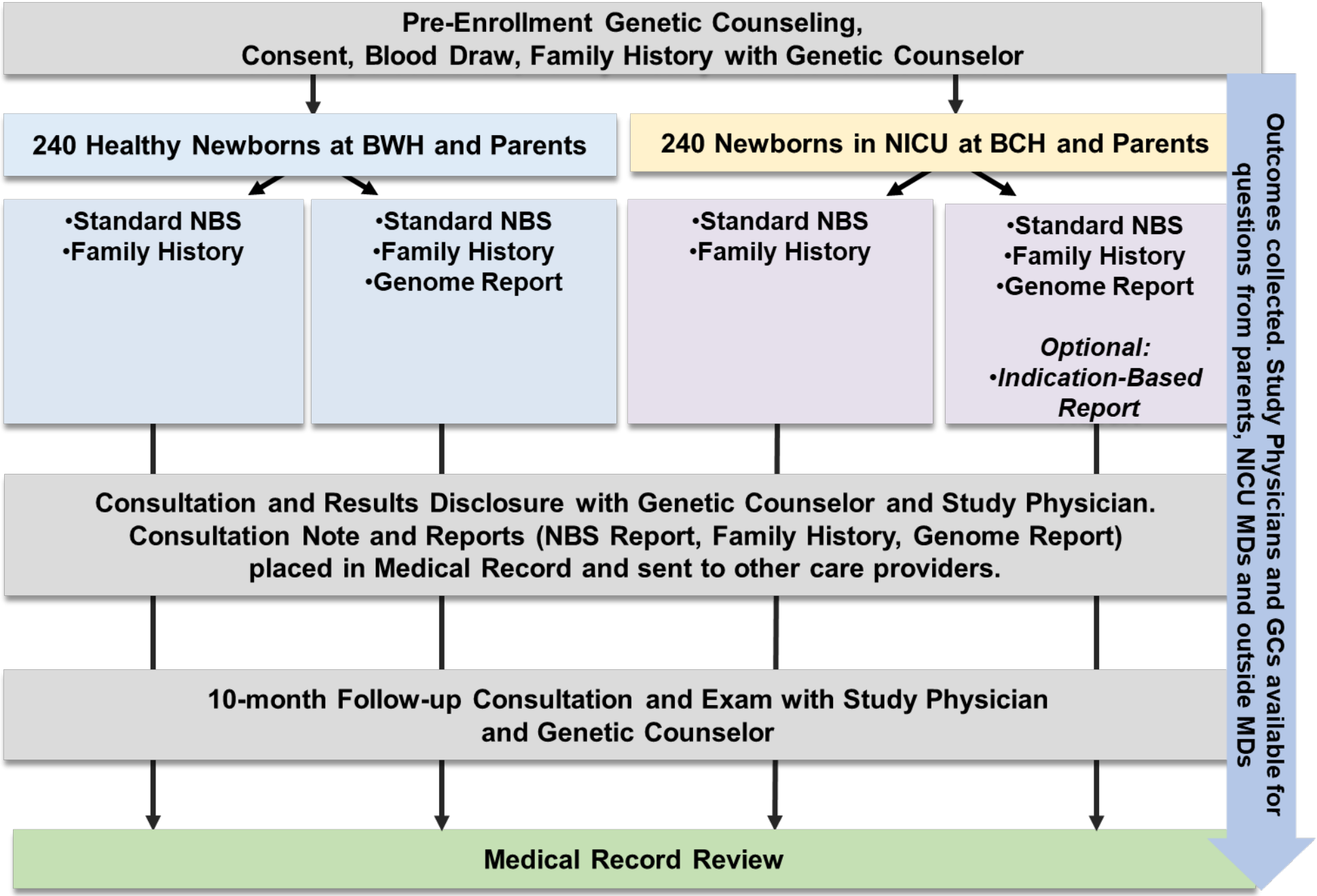
- **Question A)** For **disorders currently screened for in newborns**, how can genomic sequencing replicate or augment (e.g., make more accurate, comprehensive or inexpensive) known newborn screening results?
- **Question B)** What knowledge about **conditions not currently screened for in newborns** 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.

3 Components Required

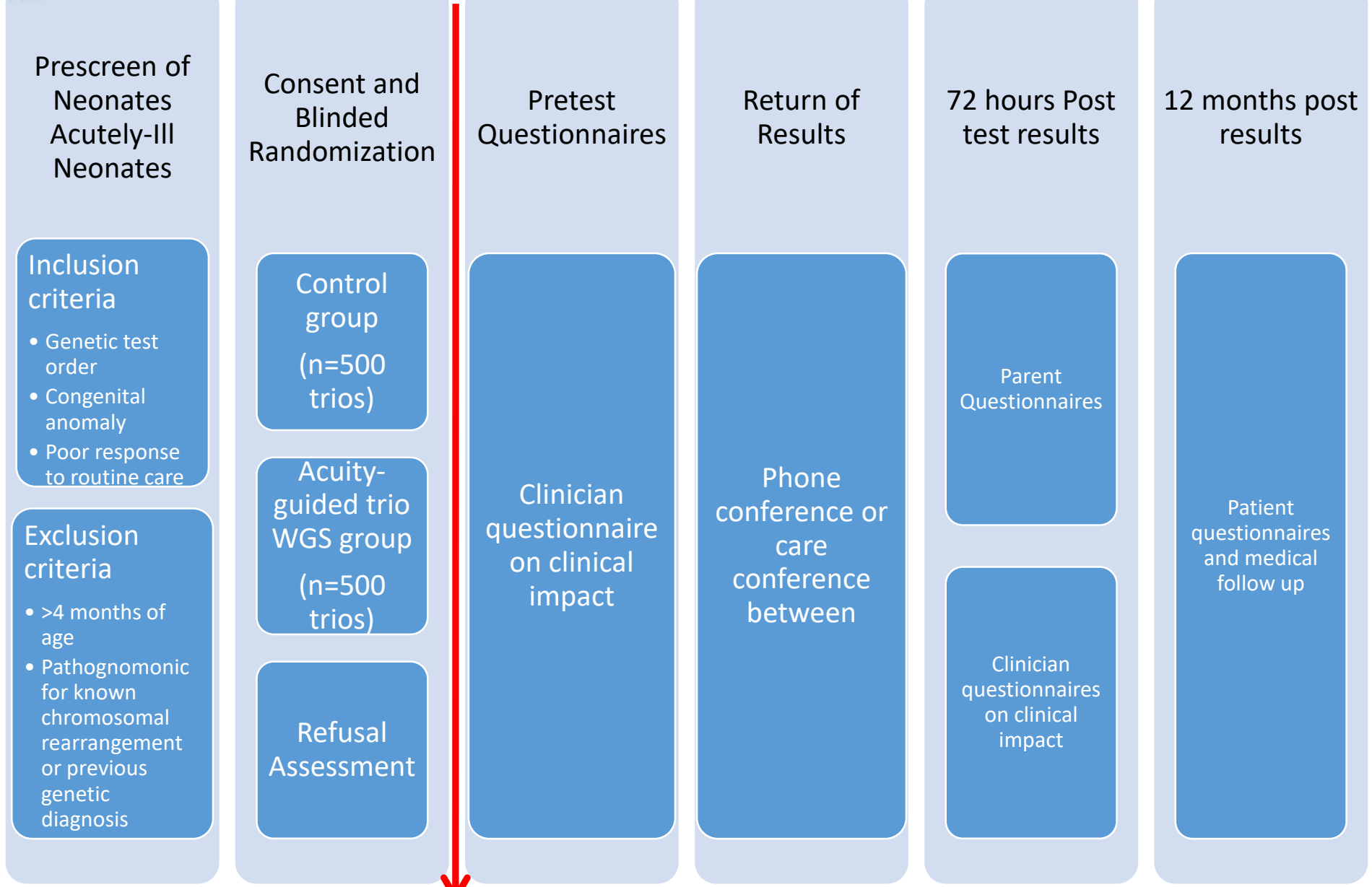


Principal Investigators	Institutions	Title
Robert Green Alan Beggs	Brigham and Women's Hospital Boston Children's Hospital	BabySeq: Genome Sequence-Based Screening for Childhood Risk and Newborn Illness
Stephen Kingsmore	Rady Children's Hospital, San Diego Children's Mercy Hospital, Kansas City	Clinical and Social Implications of 2-day Genome Results in Acutely Ill Newborns
Jennifer Puck Barbara Koenig Pui-Yan Kwok	University of California San Francisco	NBSeq: Sequencing of Newborn Blood Spot DNA to Improve and Expand Newborn Screening
Cynthia Powell Jonathan Berg	University of North Carolina at Chapel Hill	NC NEXUS: North Carolina Newborn Exome Sequencing for Universal Screening

Brigham & Women's Hospital–Boston Children's Hospital (BWH-BCH) Project Overview



Children's Mercy-Rady Children's



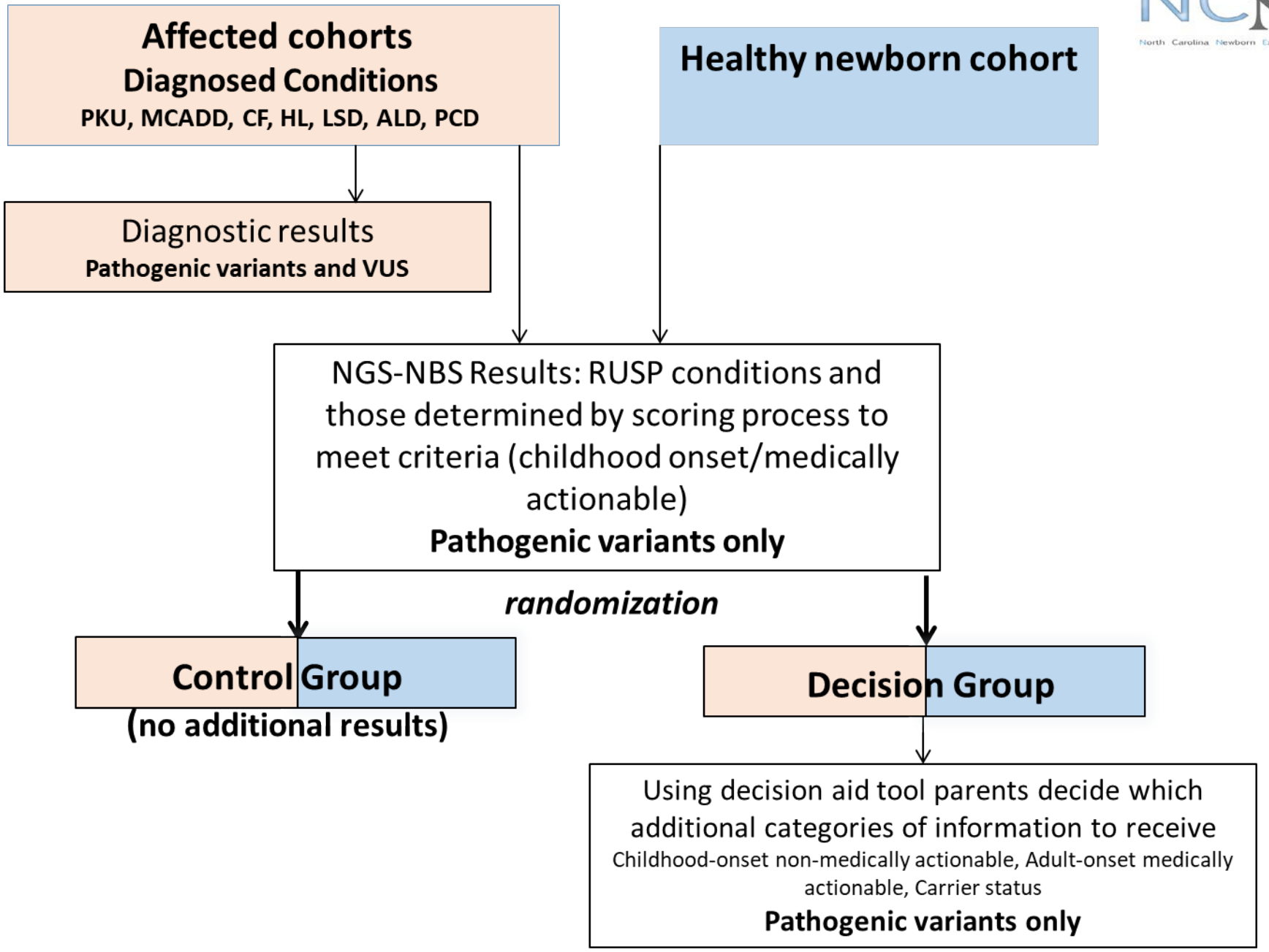
University of California- San Francisco (UCSF) Project Overview

- Whole exome sequencing of dried blood spots from CDPH biobank from infants with known conditions identified through standard newborn screening
  - Annotate variants in a set of ~90 primary metabolic genes and additional genes identified through pathway analysis

- Examination of variants in selected immunodeficiency genes obtained by Whole Exome Sequencing of newborn blood spots from patients who are suspected of having primary immunodeficiencies not identified by TREC newborn screening.

- How will next-generation sequencing enhance, challenge, or transform traditional state-mandated NBS?

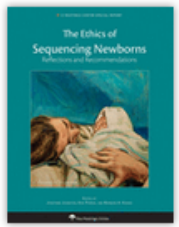
University of North Carolina (UNC) Project Overview



Wall Street Journal July 7, 2014: “Over the course of the next few decades, the availability of cheap, efficient DNA sequencing technology will lead to a medical landscape in which each baby’s genome is sequenced, and that information is used to shape a lifetime of personalized strategies for disease prevention, detection and treatment.”

Francis Collins, M.D., Ph.D
Director, National Institutes of Health

THE HASTINGS CENTER REPORT



Volume 48, Issue S2

The Ethics of Sequencing Newborns: *Reflections and Recommendations*

Pages: S2-outside back cover
July/August 2018

GO TO SECTION

Special Report

Article

Free Access

Sequencing Newborns: *A Call for Nuanced Use of Genomic Technologies*

Josephine Johnston, John D. Lantos, Aaron Goldenberg, Flavia Chen, Erik Parens, Barbara A. Koenig, members of the NSIGHT Ethics and Policy Advisory Board

Pages: S2-S6 | First Published: 14 August 2018

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JOHN D. LANTOS is a professor of pediatrics at University of Missouri at Kansas City and the director of the Children's Mercy Hospital Bioethics Center. His most recent book, Pre-term Babies, Fetal Patients, and Childbearing Choices, explores the changing nature of prenatal care and fetal medicine.

BARBARA A. KOENIG is a professor of bioethics and medical anthropology at UCSF. She is the director of the UCSF Program in Bioethics, which spans ethics research, clinical ethics, and education across the university's four professional schools. Her current research interests include emerging genomic technologies and the use of deliberative democracy to engage communities about research governance.