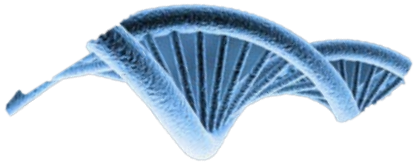
Building Bonds Between NHGRI NICHD



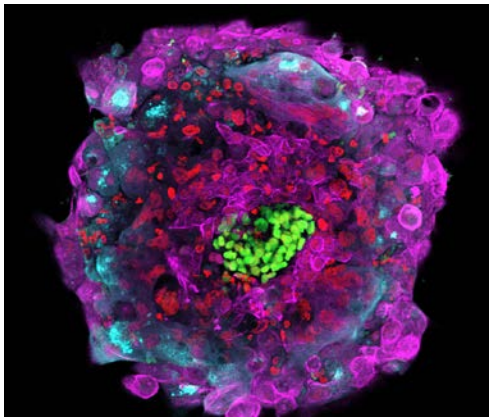
Diana W. Bianchi, M.D.

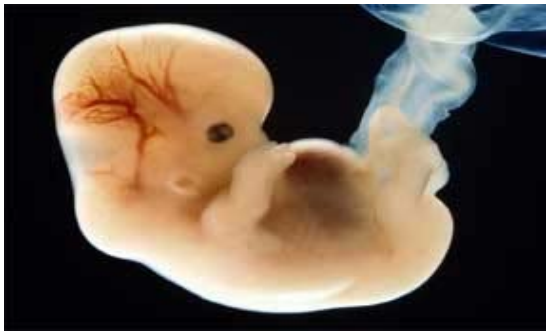
Director, NICHD

NIH *Eunice Kennedy Shriver* National Institute of Child Health and Human Development

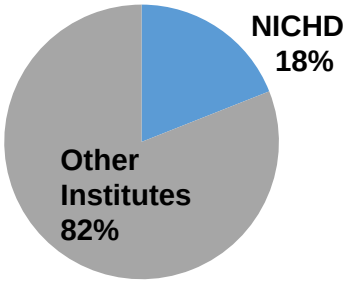
November 8, 2017

A Vision for NICHD's Future





What's In a Name?



Eunice Kennedy Shriver

National Institute of Child Health and Human Development

History of Our Mission

". . . We will look to the National Institute of Child Health and Human Development for a concentrated attack on the unsolved health problems of children and of mother-infant relationships. This legislation will encourage imaginative research into the complex processes of human development from conception to old age. . . For the first time, we will have an institute to promote studies directed at the entire life process rather than toward specific diseases or illnesses."

—John F. Kennedy, October 17, 1962

My Vision for NICHD-I

- **Define “our brand” (what is our focus?)**
  - **Communicate the message**
- **Listen to the Voice of the Patient**
- **Integrate obstetrics and pediatrics research at NICHD; take the long view (DoHaD)**
- **Advocate for personalized medicine in pediatrics, obstetrics and rehabilitative medicine**

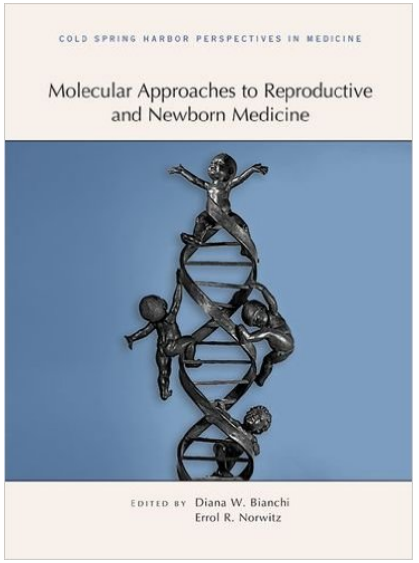
My Vision for NICHD-II

- **Stress the importance of data science and sharing to leverage our investments**
- **Analyze best way to identify trainees most likely to succeed**
- **Catalyze innovation**
- **Emphasize the “A” (for “Advice”) in the Advisory Council**
- **Build bridges between other NIH Institutes – especially with NHGRI**

Ensure Representation of NICHD Populations in Trans-NIH Initiatives

- **Pregnant women can be enrolled in Phase I**
- **Adults with intellectual disabilities can be enrolled once consent issues have been clarified**
- **Children to be enrolled in Phase II**

Building Bonds



Melissa Parisi MD PhD

NIH *Eunice Kennedy Shriver* National Institute of Child Health and Human Development

Medical Genetics Branch: Prenatal Genomics and Therapy Section

- New Lab at NHGRI
- Focus on Prenatal Treatment of Down syndrome
- Incidental Findings Following Prenatal DNA Screening

Building Bonds Between NHGRI and NICHD

- **NICHD has four ABMGG boarded clinical geneticists**
  - **Drs. Diana Bianchi, Melissa Parisi, Forbes (“Denny”) Porter and Constantine Stratakis**
- **Opportunities for collaborative training activities and clinical research**

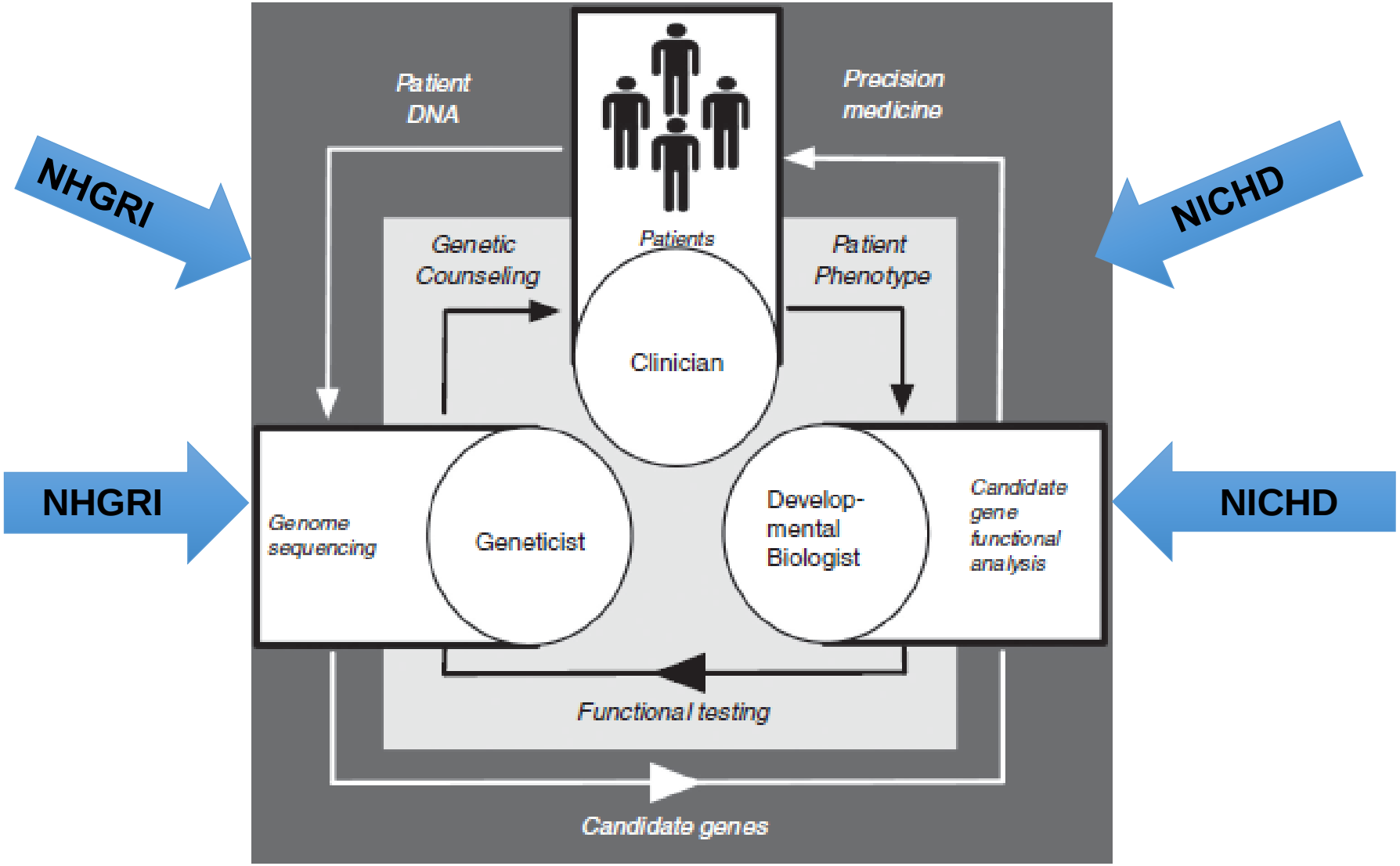
Examples of Existing NHGRI-NICHD Collaborations

Gabriella Miller Kids First PEDIATRIC RESEARCH PROGRAM

Newborn **S**equencing **I**n **G**enomic medicine and public **H**eal**T**h (**NSIGHT**) program

ClinGen Clinical Genome Resource

UDN Undiagnosed Diseases Network



From Khoka et al. Pediatr Res doi: 10.1038/pr.2016.229

Existing Collaborations

- 8 million kids born/year with serious birth defects
- Individual birth defects phenotypes are rare and existing cohorts are small
- Leading cause of pediatric hospitalizations, medical expenses, death
- GMKF creates an interdisciplinary research infrastructure
- Congressionally-mandated program provides up to 12.6 million/year, starting in FY 2015
- NICHD is lead institute

Existing Collaborations

- **Goal is to provide well-curated medical, genomic and clinical data from a large number of children with structural birth defects or childhood cancers**
  - **By the end of 2017: 15,000 samples expected**
- **Integrate different data sets in one location and provide support for analysis**
  - **Provide easy access and analytical tool sets**
- **Generate new sequence data and facilitate deposition**
- **Other ICs involved: NHGRI, NHLBI, NCI**

Existing and Future Collaborations

Newborn **S**equencing **I**n **G**enomic medicine and public **H**eal**T**h (**NSIGHT**) program

- **Equally funded by NHGRI & NICHD**
- **Goal is to explore the challenges and opportunities associated with the use of genomic sequencing in the newborn period**
- **Compare with known newborn screening results**
- **4 awards, funded through August 2018**
- **<u>Opportunity</u>: Joint workshop to determine key questions for next funding cycle**

Opportunities for Future Collaboration

NICHD Genomic Clinical Variant Expert Curation Panels (U24) RFA-HD-17-001

- **Establish expert panels to select genes and variants associated with conditions of high priority to NICHD**
  - **Reproductive and gynecologic health**
  - **Poor pregnancy outcomes**
  - **High-risk newborn conditions**
  - **Structural birth defects**
  - **Intellectual and developmental disabilities**
  - **Susceptibility to infection**

NICHD Genomic Clinical Variant Expert Curation Panels (U24) RFA-HD-17-001

- **Goals: Systematically determine clinical significance and utility**
- **Utilize ClinGen and ClinVar tools and infrastructure to determine strength of evidence supporting clinical significance**
- **Deposit final adjudication regarding pathogenicity into ClinVar**
- **3 Expert Panels $1,000,000/year for 3 years**
- **Applications received by January 10, 2017**

Opportunities for Future Collaboration

ELSI/CEER

- **<u>Goal</u>: Establish trans-disciplinary research teams to conduct research on ELSI issues related to genetics and genomics**
- **In prior competitions NICHD provided co-funding and funded 1 CEER**
- **NICHD has signed on to some PAs if they pertain to topics of relevance to NICHD**
  - **ART, developmental disabilities, newborn screening**

Opportunities in Prenatal Genomics

"As we learn about effective interventions for genetic risk factors, and recognize that interventions early in life provide significant advantages, it will become more and more compelling to determine this information at birth."

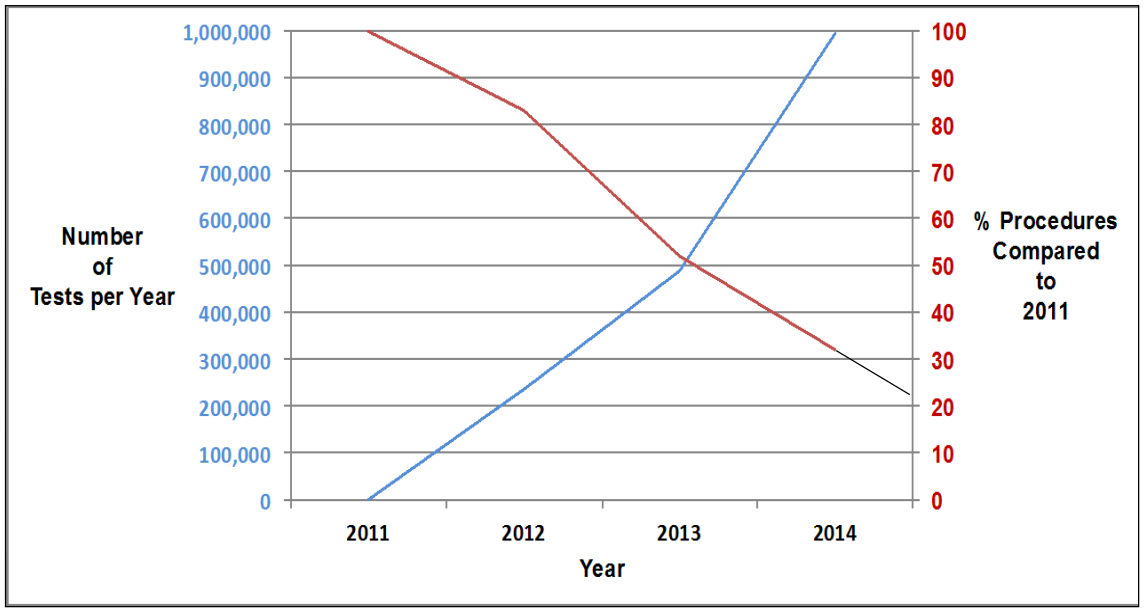
Francis Collins in *The Language of Life: DNA and the Revolution in Personalized Medicine*

Opportunities are increasingly appearing to determine this information before birth

Unique Challenges in Prenatal Genomics

- **Proband's physical "exam" is limited to anomalies detected by prenatal sonography**
- **Lack of knowledge regarding natural history of some variants**
- **Possibility of irrevocable action**
- **Roles of industry (and social media)**

Opportunity: Prenatal Genomics

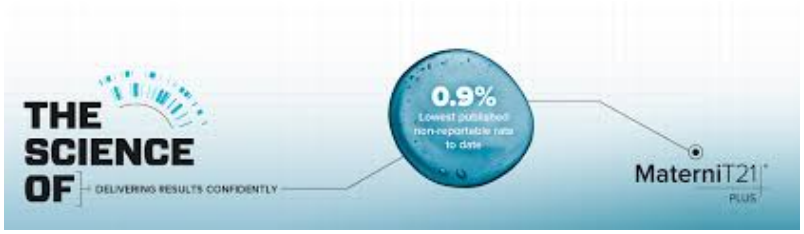


verifi™ prenatal test

Harmony™ PRENATAL TEST

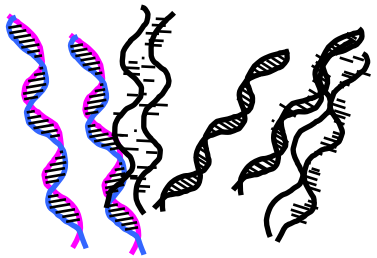
Noninvasive prenatal screening using cfDNA

natera™ Conceive. Deliver.



NIFTY®

NIPT: Sequence, Align, Count



Cell-free DNA in Maternal Plasma

~143-166 bp fragments from both pregnant woman and her fetus

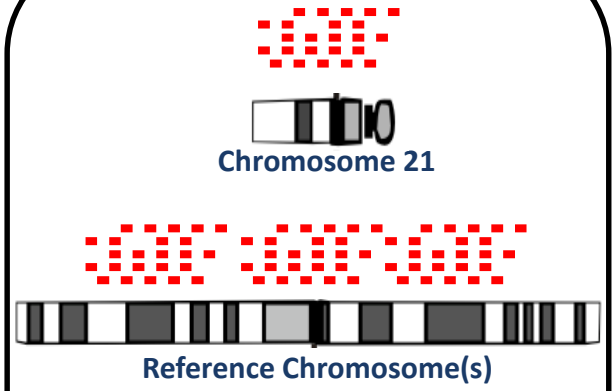
1-2 Days

CCCTTAGCGCTTTAACGTACGTAAAA
CCCTTAGCGCTTTAACGTACGTAAAA
ACGGGGTCAAAGGTTCCCACACGTCC
GACTTAAAATCGGAATCGATGCCCAA
GACTTAAAATCGGAATCGATGCCCAA
ACGGGGTCAAAGGTTCCCACACGTCC
CCCTTAGCGCTTTAACGTACGTAAAA
CCCTTAGCGCTTTAACGTACGTAAAA
ACGGGGTCAAAGGTTCCCACACGTCC

Total DNA is sequenced

25-36 base pair reads

2-3 Days

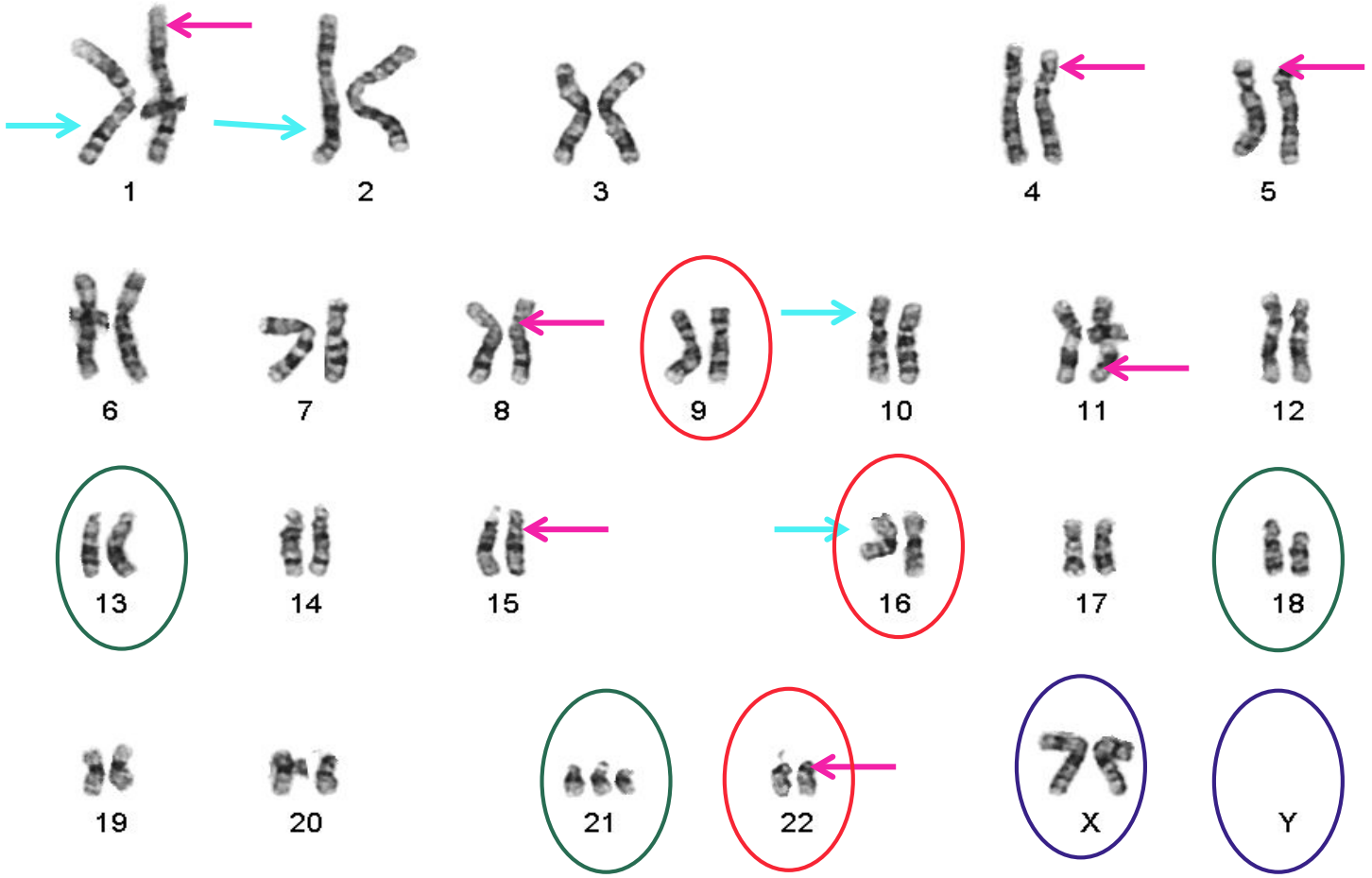


Alignment of reads

Measure counts relative to a reference

~3 Days

Rapid Progression of NIPT Test Options



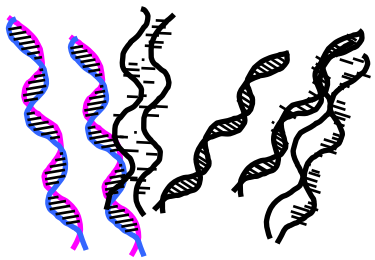
Microdeletion tests added in 2013

MaterniT GENOME

2015

WGS: Prepare, Sequence, Interpret

1-3 Days



- Obtain DNA from cells
- Fragment 200-600 bp
- Prepare libraries

4-8 Days

CCCTTAGCGCTTTAACGTACGTAAAA
CCCTTAGCGCTTTAACGTACGTAAAA
ACGGGGTCAAAGGTTCCCACACGTCC
GACTTAAAATCGGAATCGATGCCCAA
GACTTAAAATCGGAATCGATGCCCAA
ACGGGGTCAAAGGTTCCCACACGTCC
CCCTTAGCGCTTTAACGTACGTAAAA
CCCTTAGCGCTTTAACGTACGTAAAA

- Sequence aligned to reference genome
- Look for variations in DNA

9-60 Days

- Identify changes relative to reference
- Compare with parents & databases
- Remove clinically insignificant variants
- Validation
- Report variations +/- VoUS

Prenatal WES/WGS in Obstetrics

- **Baylor-Miraca: prenatal trio sequencing (since spring 2015)**
  - **2-3 week turnaround time, can provide reports in 90% of cases**
  - **100% coverage for 3463 genes in OMIM**
  - **18/52 (35%) of cases achieved a diagnosis**
- **Gene Dx: 72 products of conception**
  - **18% had definitive variants that explained phenotype**
  - **42% possible, 12% candidate, 28% were negative**

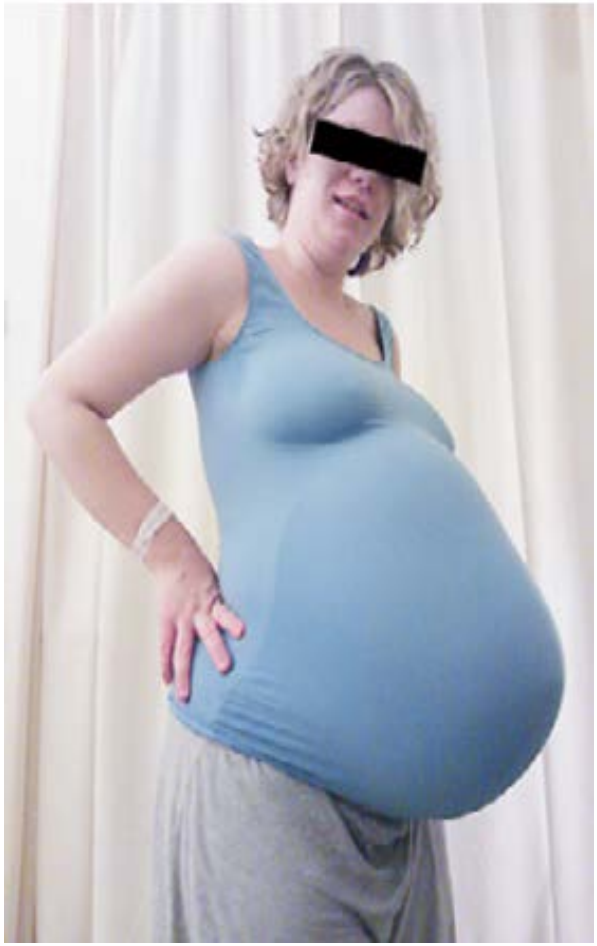
Benefits of WGS in Perinatal Care

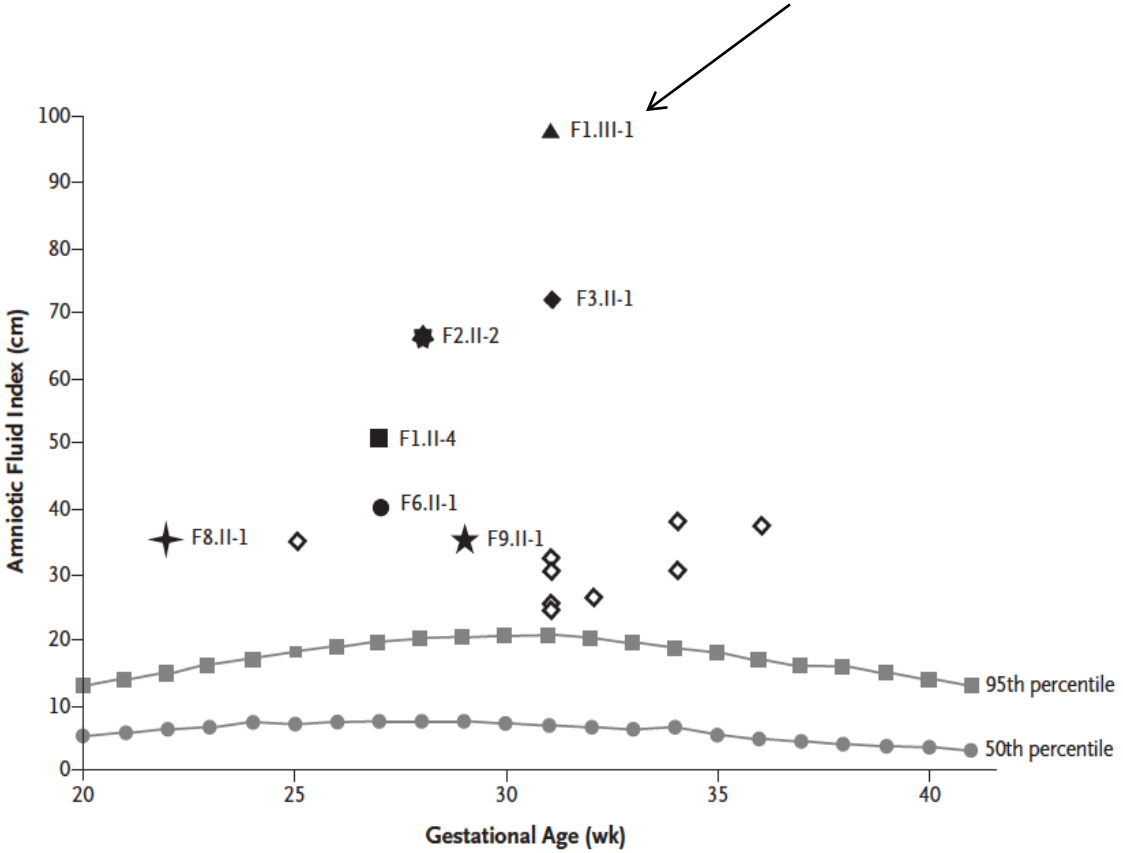
- **8042 single gene disorders (leading cause of infant deaths)**
- **Provides early warning that affects neonatal care**
  - **Metabolic disease**
- **Definitive diagnosis for fetus/newborn with anomalies and normal karyotype or microarray**
- **Better reproductive health**
  - **Genetic counseling with accurate recurrence risks**
  - **Preimplantation genetic diagnosis/ Prenatal diagnosis**

WGS Changes Management: Bartter's Syndrome

- Rare, genetically heterogeneous condition
- Renal salt wasting, hypokalemic metabolic alkalosis. Secondary hyperaldosteronism
- 2 presentations: antenatal and classical
- Antenatal: severe polyhydramnios, preterm birth
- Some antenatal cases resolve spontaneously

Antenatal Bartter's Syndrome





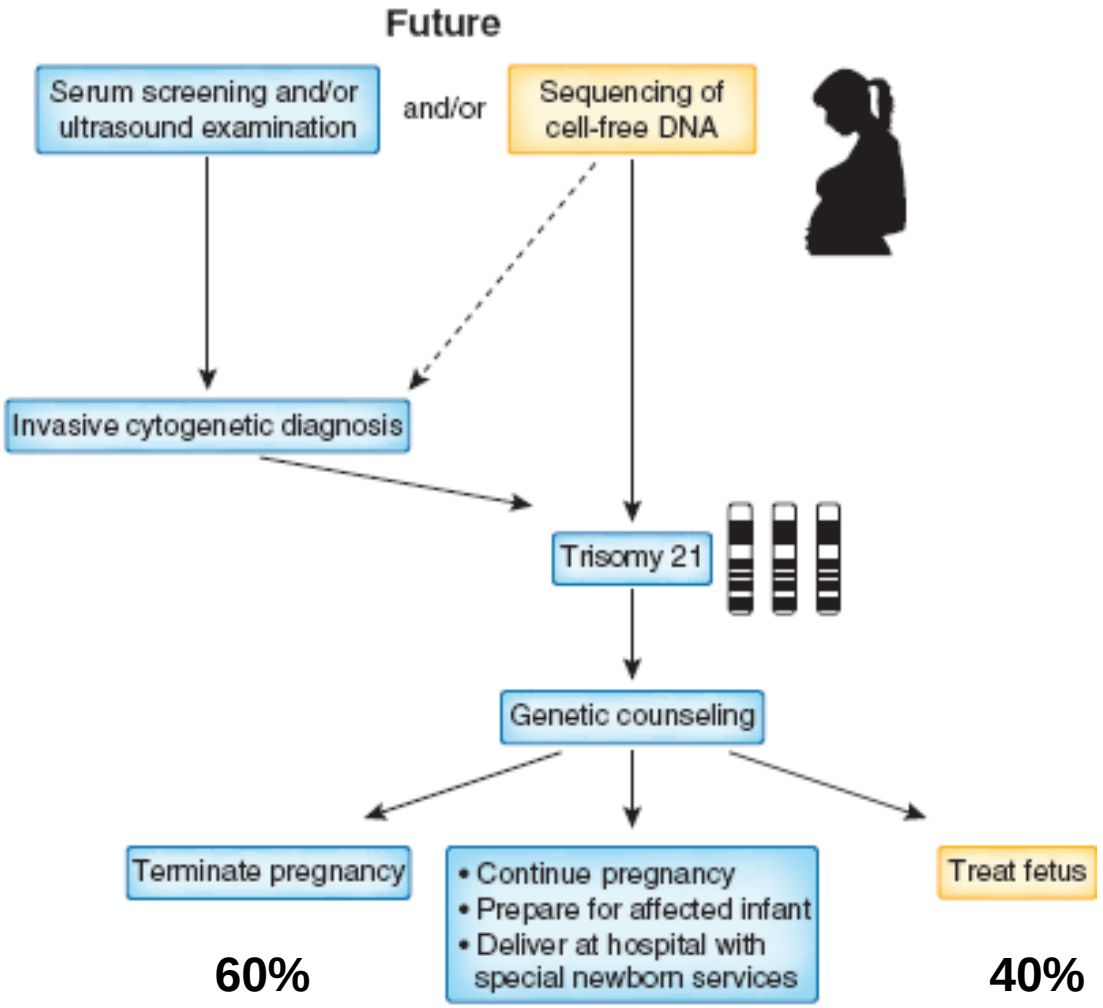
From Laghmani et al.
N Engl J Med 2016; 374:1853-1863

X-linked Bartter's Syndrome

Laghmani et al. *N Engl J Med* 2016; 374:1853-63

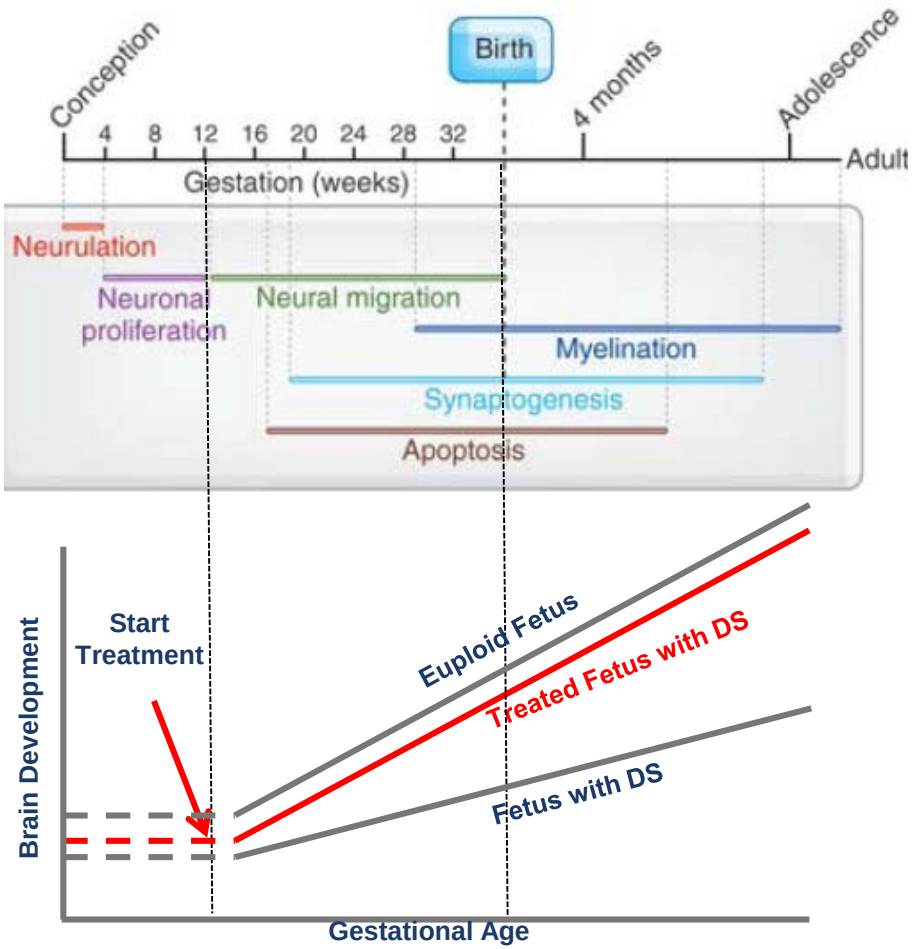
- **Distinct X-linked phenotype and gene mutations identified in *MAGED2* (maps to Xp11.2)**
- **MAGED2 expressed in ascending loop of Henle, new role in fetal renal salt absorption**
- **Management changed**
  - **Condition resolves spontaneously in survivors**
  - **Probably no need for Na, K supplements and non-steroidal anti-inflammatory drugs**
  - **Offer *MAGED2* testing to women carrying male fetuses with extreme polyhydramnios**

Opportunities for Antenatal Treatment of Down Syndrome



From: Bianchi DW, Nature Medicine 2012; 18: 1041-1051

Potential Impact of Fetal Treatment on Brain Development and Cognition in DS

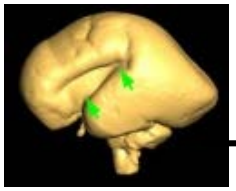


Approach to Preclinical Treatment of T21

Humans with T21

AF & Amniocytes (Slonim et al, 2009)

iPSCs & Neurons (Weick et al, 2013)

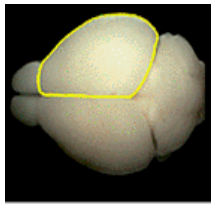


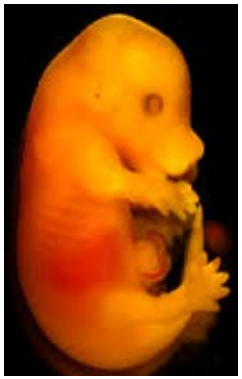
Fetal Cerebrum & Cerebellum (Mao et al, 2005)

Step I: Gene Expression Microarrays

Mouse Embryos

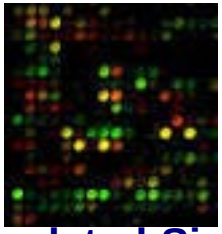
E15.5 brain



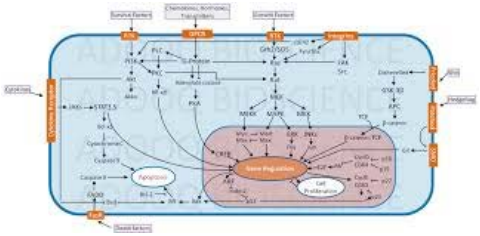


Ts1Cje, Ts65Dn, Dp16
Mouse models of DS

Step II: Differentially-Expressed Genes



Step III: Dysregulated Signaling Pathways



Summarized in Guedj et al. *Sci Rep* 2016; Sept 2 6: 32353

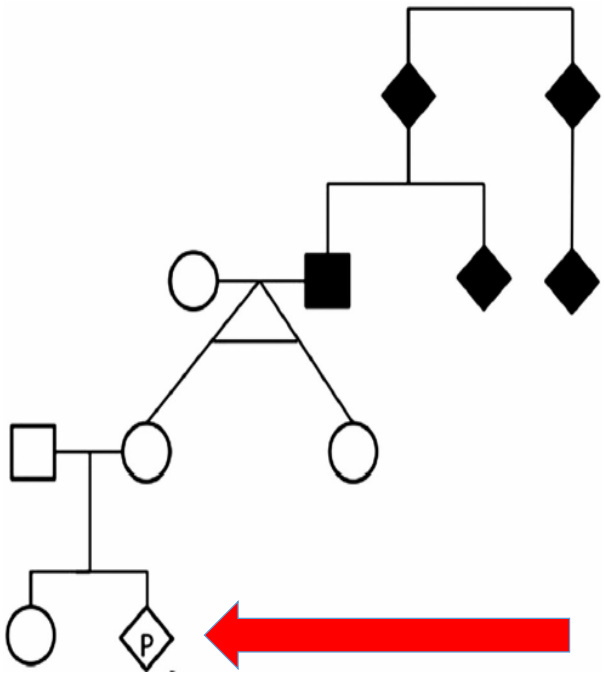
ELSI Issues Raised by Prenatal Genomics

- **NIPT: Maternal incidental findings**
  - **(Lack of) consent**
  - **CNVs (clinically significant and non-significant)**
  - **Mosaicism (sex chromosome and autosomal aneuploidy)**
  - **Cancer—when to suspect, what to do**
- **Possibility of taking irrevocable action**

False Positive Results Due to Maternal CNV on 21

Meschino et al. *Prenat Diagn* 2016; doi: 10.1002/pd4783

- **37 yo G2P1 woman at 21 weeks'**
- **1st trimester screen negative (1/280)**
- **Fetal anatomy scan showed bilateral CPCs and borderline cerebral ventriculomegaly**
- **Given choice of amnio or NIPT**
- **NIPT positive for trisomy 21**
- **Partial duplication of 21q21.1**
  - **CNV outside of DS critical region, but includes *APP***



Listen to the Voice of the Patient

Patient Advocacy Groups at NIPT Stakeholder Meeting July 2015

Summary

- **NHGRI's mission is to understand the structure and function of the human genome and its role in health and disease**
- **Arguably, understanding the human genome in the context of human development and early childhood disease will have the greatest impact**
- **Widespread implementation of prenatal genomic screening is the biggest success of genomic medicine, with many ELSI concerns**
- **Numerous opportunities to build bonds.**
- **Next step: meeting of key extramural leaders**

Thank You and Questions?

Endocrinology and Metabolism Rotation at Clinical Center,
circa 1979