

Ultrasound in the Molecular Era

Reclaiming Its Essential Role in Fetal Diagnosis

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22nd Annual High-Risk Fetal Imaging & Perinatal Update | October 9, 2026

Disclosure

No relevant financial relationships to disclose.

Learning Objectives

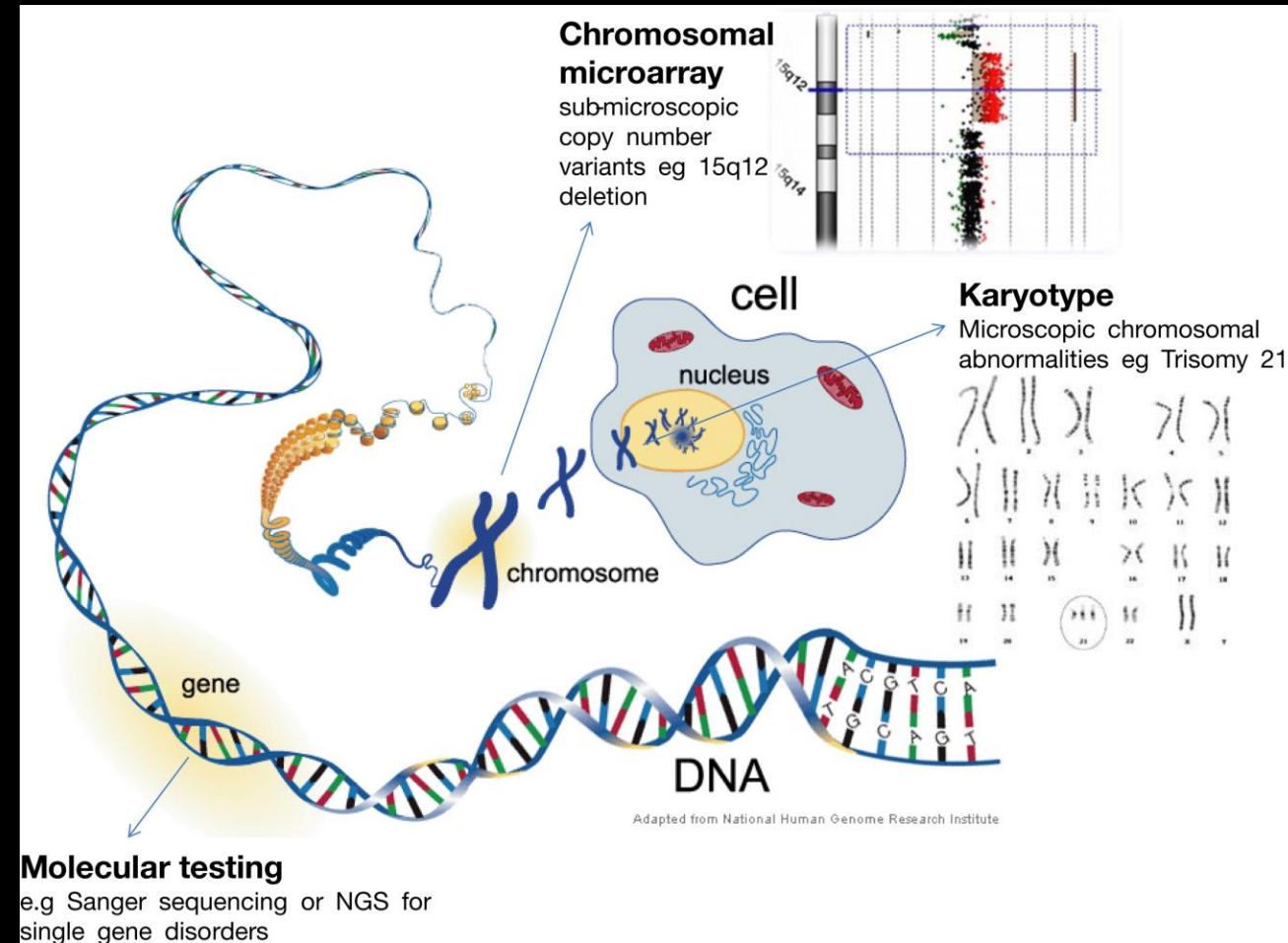
- Describe current and emerging molecular genetic testing options, and recognize their diagnostic scope and limitations.
- Identify ultrasound phenotypes and anatomic markers that signal conditions not routinely detected by conventional cell-free DNA screening — and recognize when broader genetic testing is indicated.
- Integrate sonographic findings with molecular testing strategy to optimize diagnostic yield and inform family counseling in the setting of abnormal ultrasound or borderline screening results.

The question I am often asked as an MFM-Geneticist

What findings would prompt you to recommend diagnostic testing if NIPT is low risk?

Types of Genetic Diagnoses

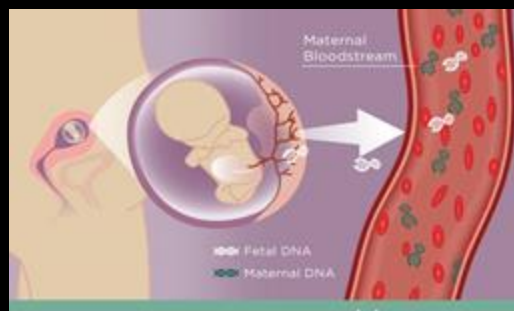
- Microscopic aberrations: trisomies, large deletions/duplications (10Mb)
- Submicroscopic aberrations: microdeletion/microduplications (100Kb)
- Genetic aberrations: single gene disorder



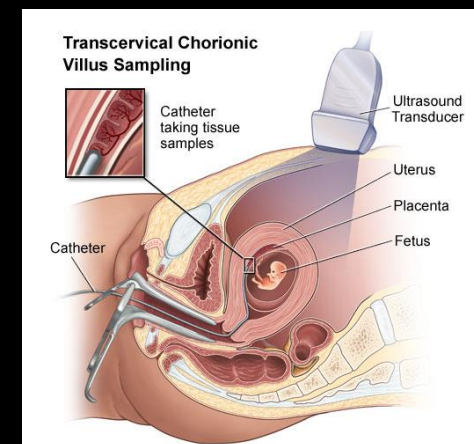


Screening vs. Diagnostic Testing

- Screening:
 - Identify high-risk population
 - Non-invasive
 - Possibility of false positive and negative
 - Residual risk
- Example:
 - Ultrasound
 - Serum screen
 - NIPT



- Diagnostic:
 - Definitive diagnosis
 - Invasive
 - Yes/No answer
 - Risk of pregnancy loss
- Example:
 - Chorionic Villus Sampling
 - Amniocentesis



What can I NIPT screen for these days?

- Common aneuploidies
 - Copy number variations (CNV)
 - Autosomal dominant single gene disorder (few skeletal dysplasias, Noonan syndrome etc)
 - Autosomal recessive single gene disorder (CF, SMA)
 - RBC antigen
 - Platelet antigen
-
- Ultimately, these are screening options

NIPT for common aneuploidies

Trisomy	Sensitivity	Specificity	PPV (general population)
T21 (Down)	~99%	>99.9%	~80–90%
T18 (Edwards)	~94–97%	>99.9%	~50–80%
T13 (Patau)	~90–100%	>99.9%	~30–50%

- Reasons for false positive: analytical error, confined placental mosaicism
- **SMFM/ACOG (2025)** recommends NIPT for the common aneuploidies be made routinely available to all obstetrical patients regardless of baseline risk

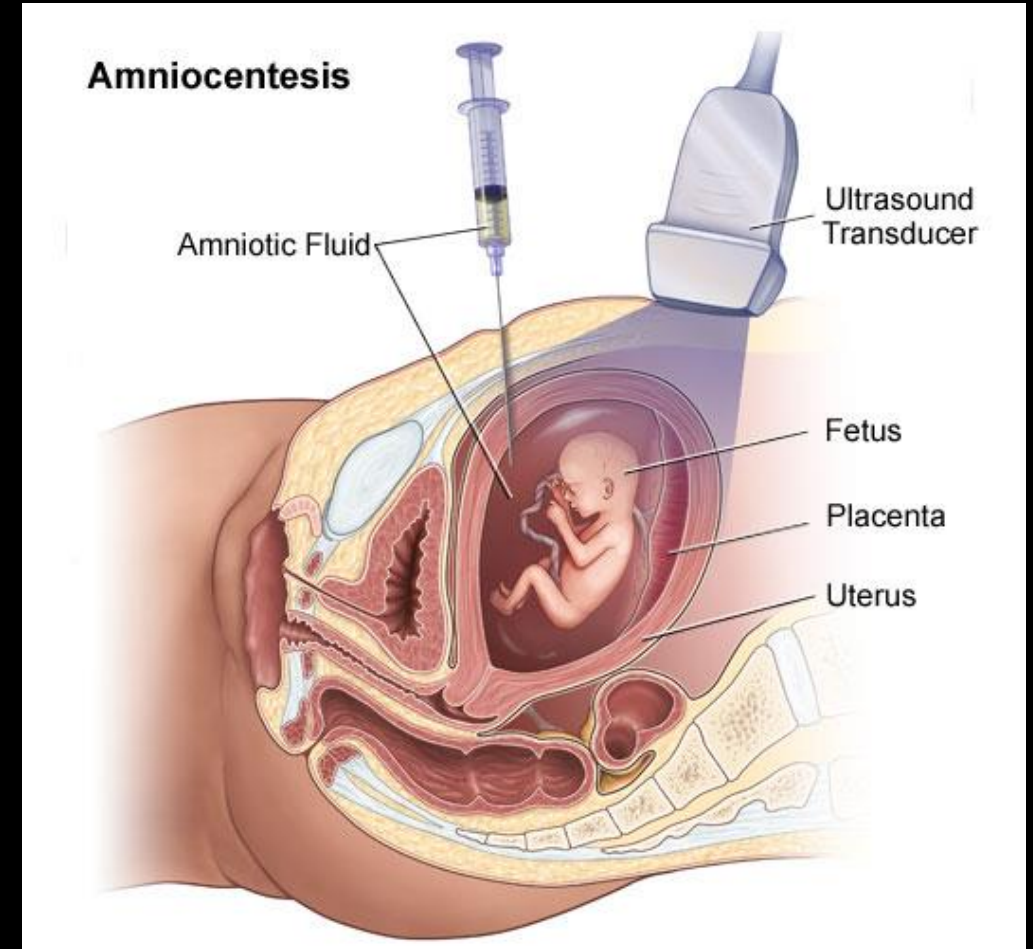
NIPT for CNV

Condition	Approximate prevalence	Reported PPV (cfDNA)	Clinical comment
22q11.2 (DiGeorge)	~1 : 1,000	~50% (higher with newer assays)	Actionable, CPM is rare
1p36 deletion	~1 : 5,000–10,000	Often <15%	Rare condition; prevalence drives poor PPV
Cri-du-chat (5p–)	~1 : 15,000–50,000	Single digits	Rare condition; prevalence drives poor PPV
Prader-Willi / Angelman (15q)	~1 : 15,000–25,000 each	Variable, often <20%	Most cases involve UPD, not deletion
Wolf-Hirschhorn (4p–)	~1 : 50,000	Single digits	Rare condition; prevalence drives poor PPV

NIPT for Single Gene Disorders

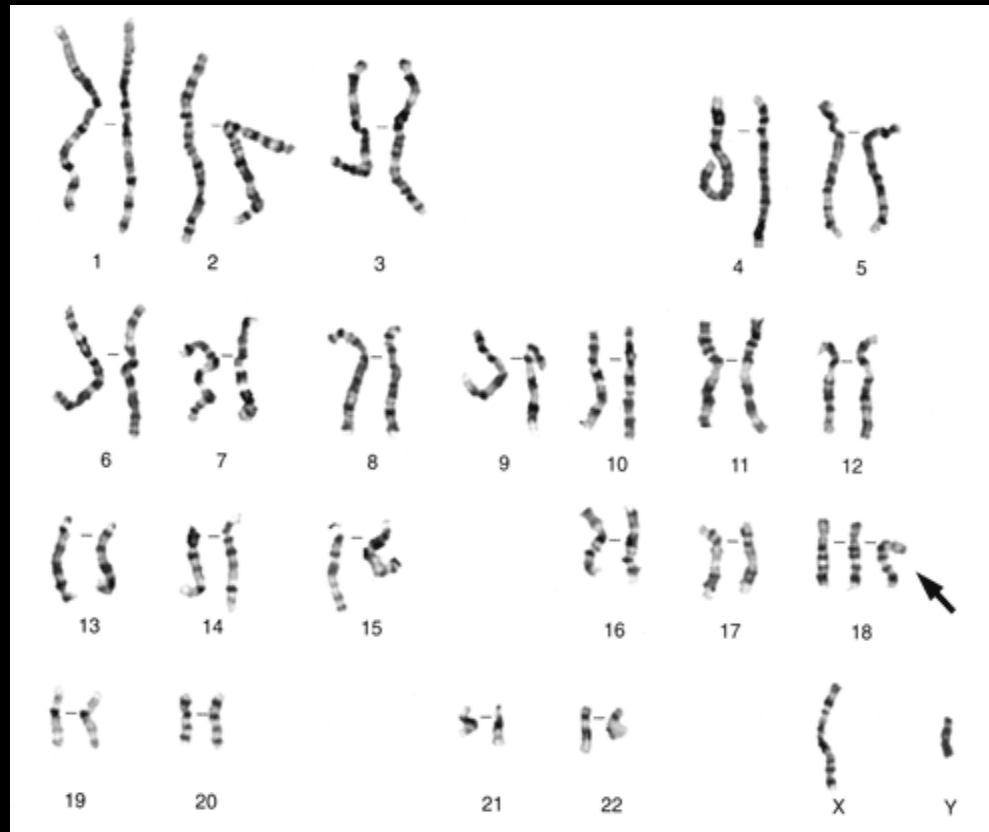
- For Autosomal Dominant (AD) conditions
 - Select skeletal disorders, craniosynostosis, RASopathies, other disorders
 - Performance less well studied
- For Autosomal Recessive (AR) conditions
 - CF, SMA, Thalassemia, Canavan, MCADD, Tay Sach, SLOS, PKU etc
- Limited data on performance

Diagnostic options



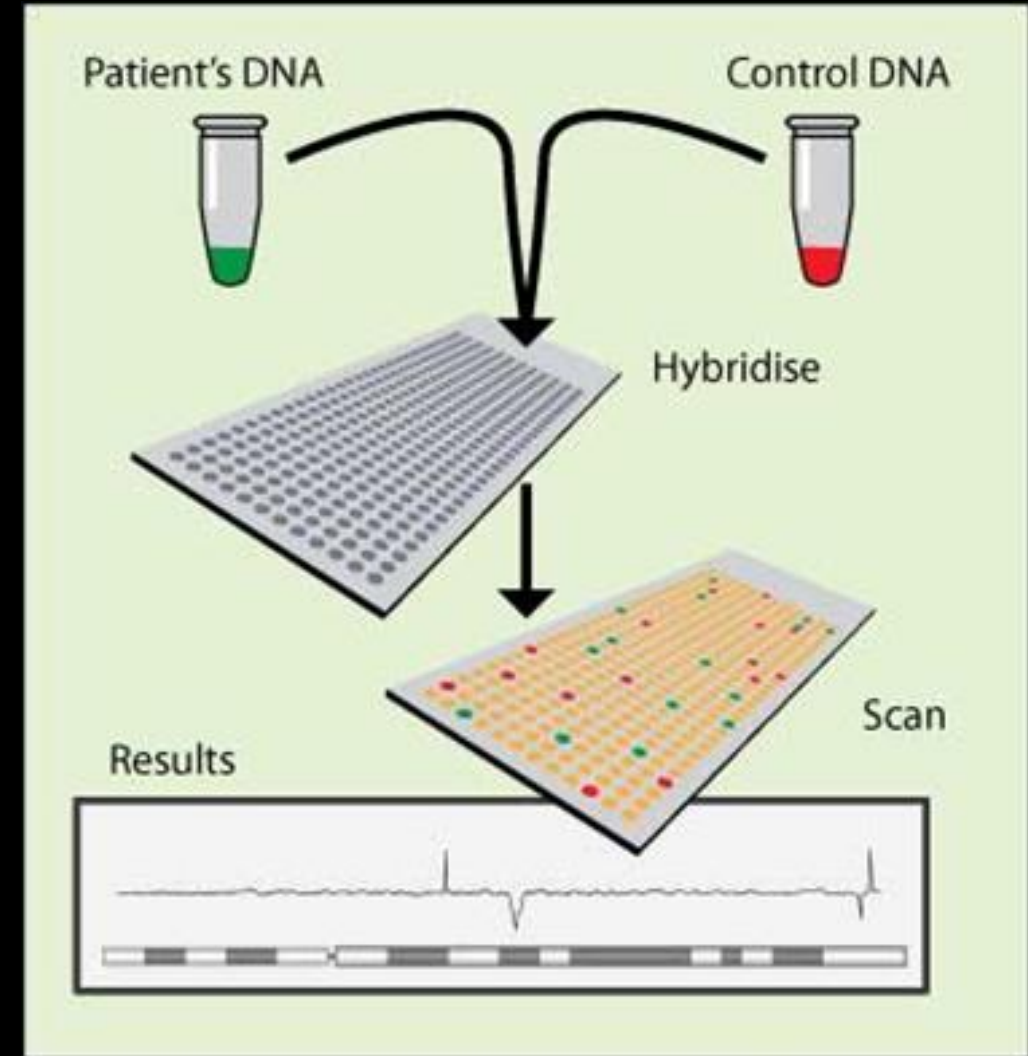
Fetal Karyotype

- Classically used to diagnose fetal aneuploidy
 - Also detects large rearrangements, deletions, and duplications (>7 Mb)



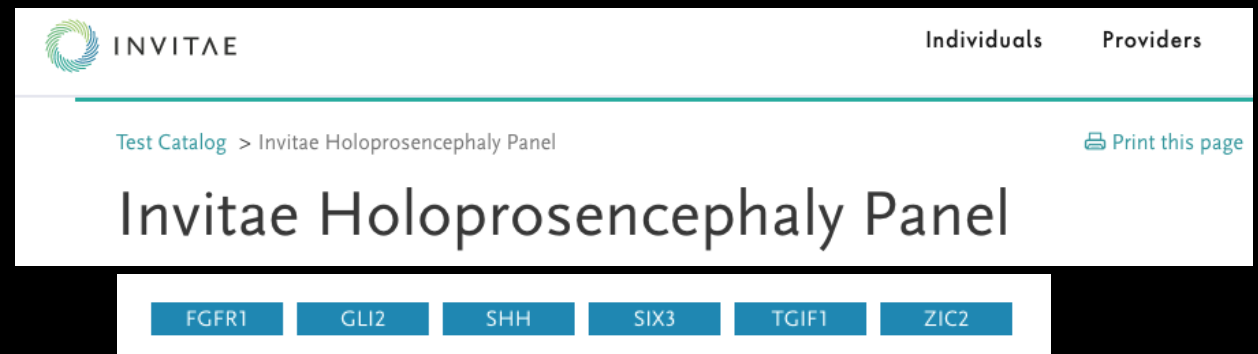
Prenatal Chromosome Microarray

- Detects smaller (~100kb) deletions or duplications of chromosomal material
 - Many benign copy-number variations (CNVs); many variants of uncertain significance (VUS)
- Compare fetal DNA against a reference genome via a microchip-based reaction
 - SNPs also used to detect uniparental disomy



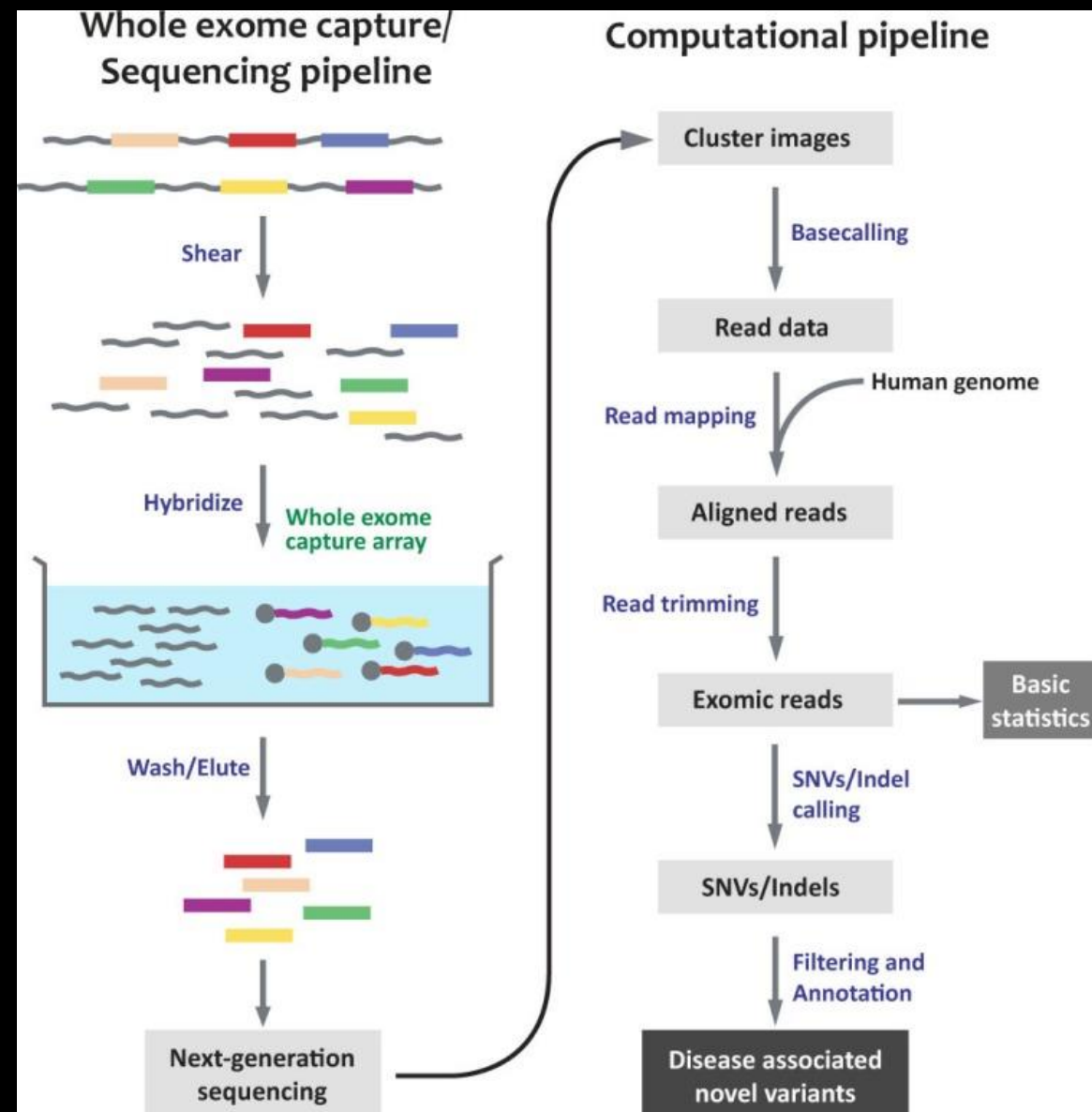
Gene Sequencing Panel/Targeted testing

- Assess multiple potential genetic causes of disorders
- Phenotype-directed
- Eg:
 - Skeletal dysplasia panel
 - Noonan panel
 - Holoprosencephaly panel



Exome/Genome Sequencing

*Exome: protein-coding regions of the genome
2% of genome, 85% of known diseases*



Goh et al, 2012

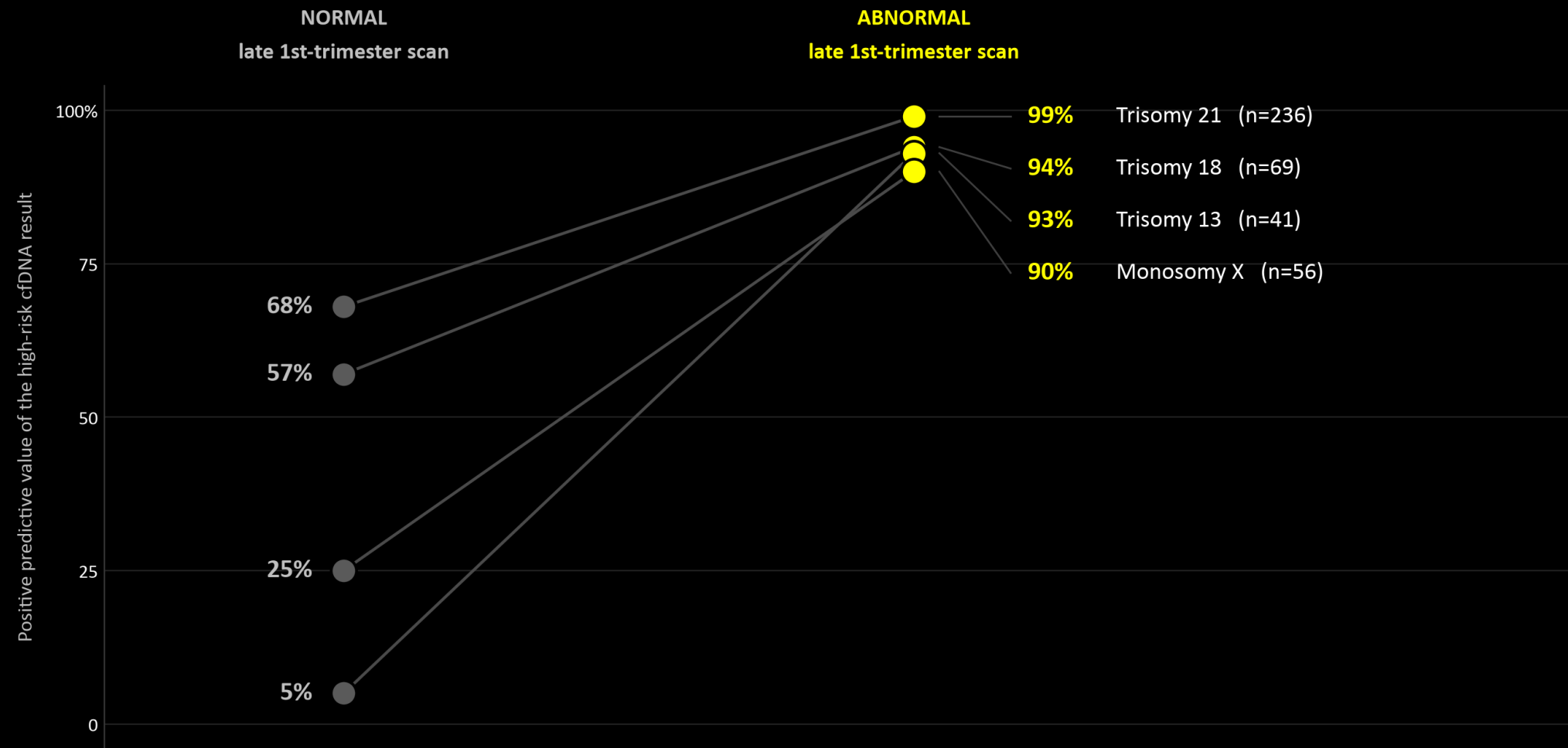
Wow! So many tests for so many things now. Do we still need ultrasound?

ABSOLUTELY!!!!!!!!!!!!

Yield is a function of phenotype

Ultrasound is your prenatal phenotyping tool

Ultrasound Improves the PPV of NIPT



Yield of prenatal genome sequencing varies widely by phenotype

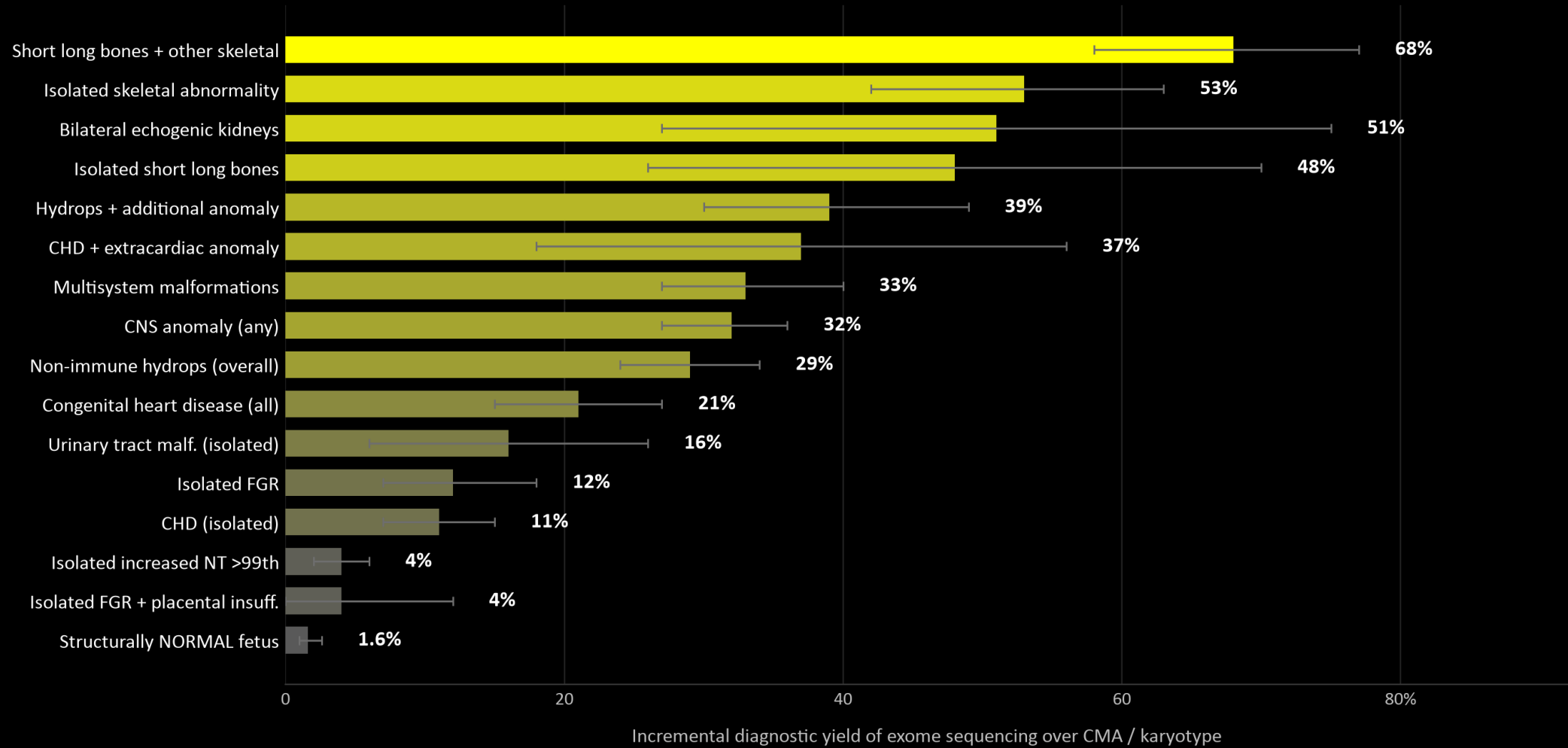
42%

Yield of genome in well characterized phenotype

15%

Yield of genome in unselected “any anomalies”

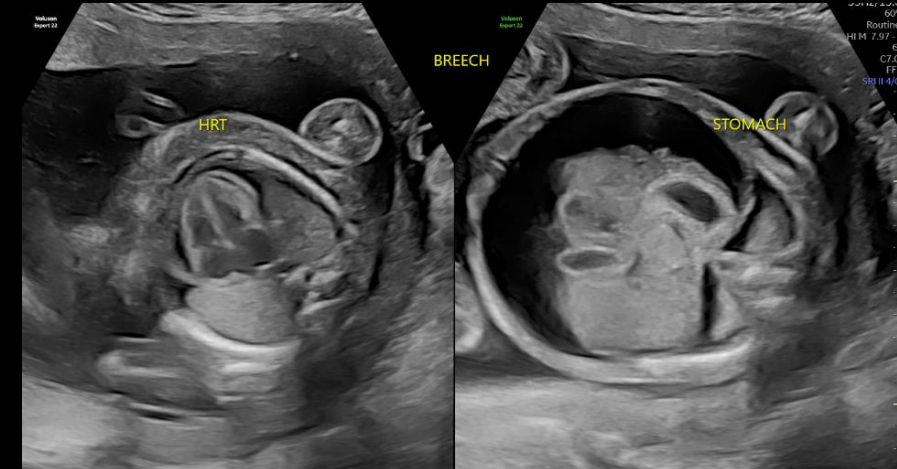
Exome Yield by Sonographic Phenotype



Mone 2023; Mellis 2022; Sonner 2024; Blayney 2024; Pauta 2022 (x2); Mone 2021 (x2); Sparks 2020; Pauta 2023; Sotiriadis 2025. Bars show incremental yield over CMA/karyotype; whiskers are 95% CI.

Non-Immune Hydrops

- **Roughly one in three cases has a monogenic cause — 29% across the pooled literature, 29% in the UCSF prospective series**
- RASopathies are the single largest group: 30% of all diagnoses, PTPN11 most common
- Then inborn errors of metabolism and musculoskeletal disorders (11% each); lymphatic, neurodevelopmental, cardiovascular and hematologic (8% each)
- 68% autosomal dominant — and 88% of those are de novo, so family history is reassuringly useless
- **63% of RASopathy cases presented as ISOLATED hydrops, with no other anomaly on the scan**
 - Isolated hydrops still yields 21%; hydrops with another anomaly yields 39%



Abnormal Nuchal Translucency



Sequencing Yield in Increased Nuchal Translucency

Incremental diagnostic yield of exome/genome sequencing over karyotype/CMA

Population	Incremental yield	Source
Isolated increased NT (meta-analysis)	~4%	Pauta et al, Ultrasound Obstet Gynecol 2022
Isolated increased NT, normal anatomy (meta-analysis)	3.87%	Di Girolamo et al, J Matern Fetal Neonatal Med 2023
NT ≥3.5 mm (WES, China cohort)	10.42% (10/96)	Zhou et al, Am J Obstet Gynecol 2025
NT thickening / cystic hygroma, after negative CMA	34.3% (12/35)	Zheng et al, Sci Rep 2024
Isolated NT vs NT + structural anomalies (Mellis)	1.8% vs 26%	Mellis et al, Prenat Diagn 2022

Yield tracks NT magnitude — negligible below 3.0 mm, 5–10% at 3.0–3.5 mm — but associated structural anomalies are the strongest driver by far.

Yield in Fetal Growth Restriction

12%

Isolated FGR

146 fetuses, 8 studies

Pauta et al, 2023

4%

Isolated FGR with placental insufficiency

95% CI -5 to 12

Mone et al, 2023

FGR with additional structural anomalies, by contrast, yields 30%.

Yield of Genome Sequencing in Sonographically Normal Fetus

1.6%

Incremental exome yield in a structurally normal fetus

Pooled across 4 studies and 1,916 fetuses with normal karyotype or microarray. Most variants were de novo in autosomal dominant genes. The probability of a variant associated with severe disease was 0.5%.

A normal scan is not a guarantee. But it is, by a wide margin, the strongest negative predictor we have.

So, what is the answer to THE question?

- What findings would prompt you to recommend diagnostic testing if NIPT is low risk?
- Any findings probably will slightly increase your risk for single gene disorder. But the highest yield would be the complex anomalies:
 - Thick NT + structural anomalies
 - FGR + VSD
 - Clubfoot + ventriculomegaly

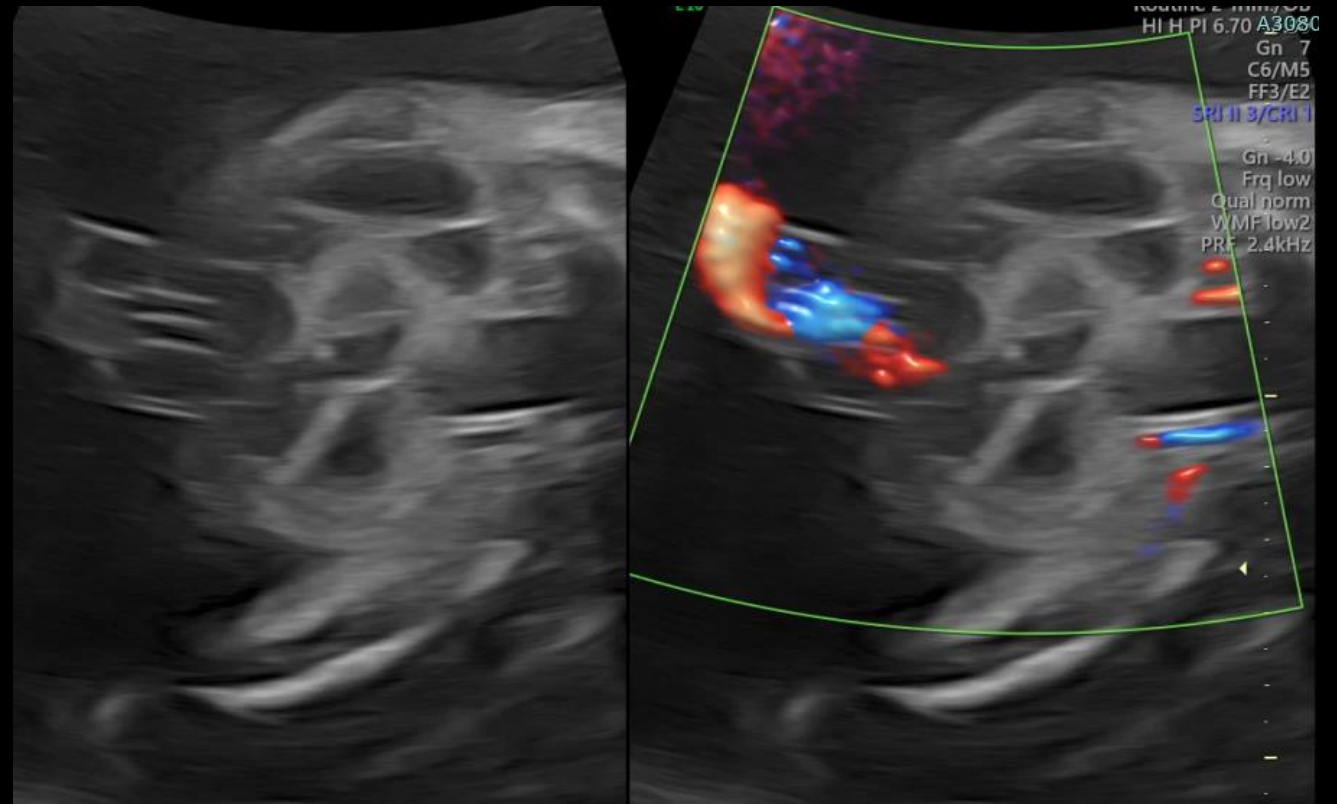
CASE EXAMPLES

Case #1

28 y/o G2P1000 presenting at 24 weeks 2 days

- For completion of anatomy
- Anatomy previously normal
- Had prior child with bowel dilation and ended with neonatal demise

Ultrasound finding →



Genetic Testing Results

Opted for amniocentesis

- Normal FISH for chromosome 13, 18, 21 and XY
- Karyotype 46,XY
- Chromosomal Microarray – no significant CNVs
- Congenital Diarrhea Gene Panel:
 - Pathogenic variants in SLC26A3
 - Associated with congenital diarrhea

Coding variant 1: c.571-1G>A

Amnio Acid variant: Splicing variant

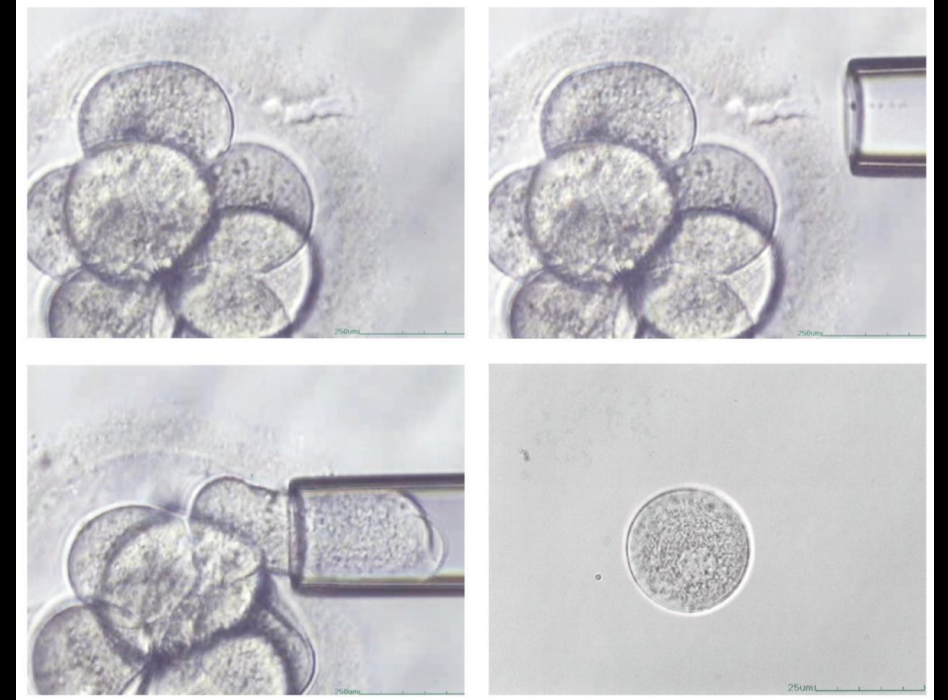
Classification: Pathogenic

Coding variant 2: c.1177G>T

Amnio Acid variant: p.Gly393Trp

Outcomes Case #1

- Prenatal counseling by GI and NICU
- Congenital diarrhea is associated with high volume diarrhea with chloride loss
- Outcome is favorable with proper management
- Once the child was born, TPN was started to maintain electrolytes
- Prevented similar outcome as previous child
- Plan for prenatal diagnosis/PGT-M with next child



Case #2

**36 y/o G1P0 presenting at 11 weeks
2 days for NT scan**

- No medical/surgical history
- No family history
- Avid mountain hiker
- First trimester US finding →



Case #2

- Repeat US at 16 weeks → normal bladder
- Repeat US at 20 weeks → normal anatomy, LGA 92%, mild polyhydramnios
- Repeat US at 24 weeks → LGA 97%, moderate polyhydramnios
- Amniocentesis, normal FISH, karyotype and CMA
- PTL at 26 weeks with severe polyhydramnios

EFW (Hadlock)		Value	Range		Age	Range	GP	Hadlock
AC/BPD/FL/HC		428g (15oz)	± 62g				-----	97.4%
2D Measurements	AUA	Value	m1	m2	m3	Meth.	GP	Age
BPD (Hadlock)	✓	5.08 cm	5.08			avg.	-----	90.9% 21w3d
HC (Hadlock)	✓	18.05 cm	18.05			avg.	-----	57.5% 20w3d
AC (Hadlock)	✓	18.02 cm	18.02			avg.	-----	98.6% 22w6d
FL (Hadlock)	✓	3.22 cm	3.20	3.24		avg.	-----	38.0% 20w0d
HL (Jeanty)	■	3.01 cm	3.02	2.99		avg.	-----	44.6% 19w6d
Cereb (Hill)	■	2.28 cm	2.28			avg.	-----	95.3% 21w1d
CM		5.33 mm	5.33			avg.		
Vp		5.84 mm	5.84			avg.		
NF		5.02 mm	5.02			avg.		
NBL (Sonek)		5.35 mm	5.35			avg.	-----	6.1%



BLADDER

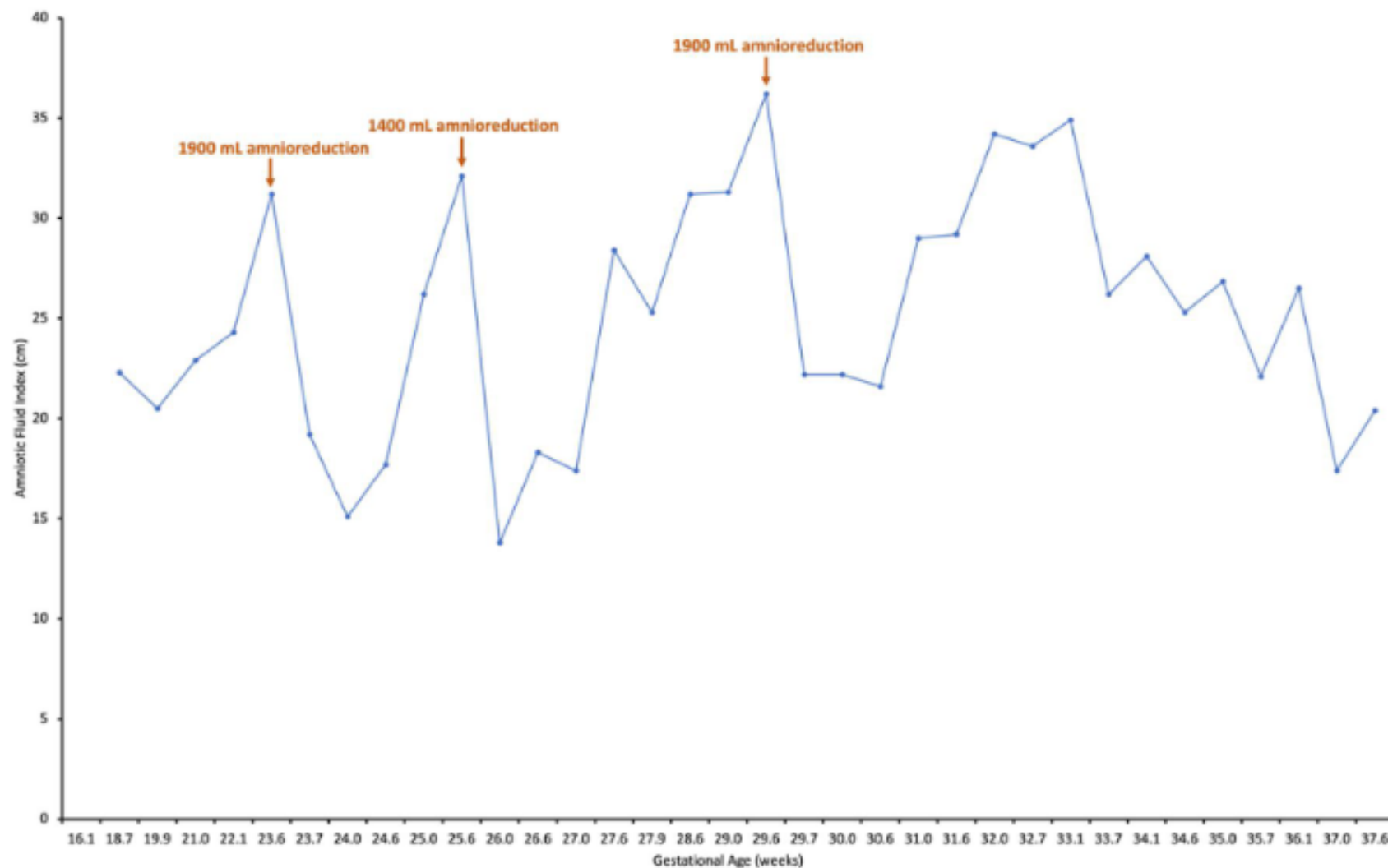
Genetic Testing Results

Given unclear phenotypes → Whole exome sequencing:

**#. VUS *MAGED2* c.1337G>A p.Arg446His, maternally-inherited, X-Linked
Bartter Syndrome**

**The lack of ultrasound phenotype outside of LGA and polyhydramnios
increased our suspicion on pathogenicity of this variant**

Successful antenatal treatment of MAGED2-related Bartter syndrome and review of treatment options and efficacy



Outcomes Case #2



Case #3

32 y/o G2P10001 referred at 32 weeks for complex arrhythmia

- No medical/surgical history
- No family history
- US finding →

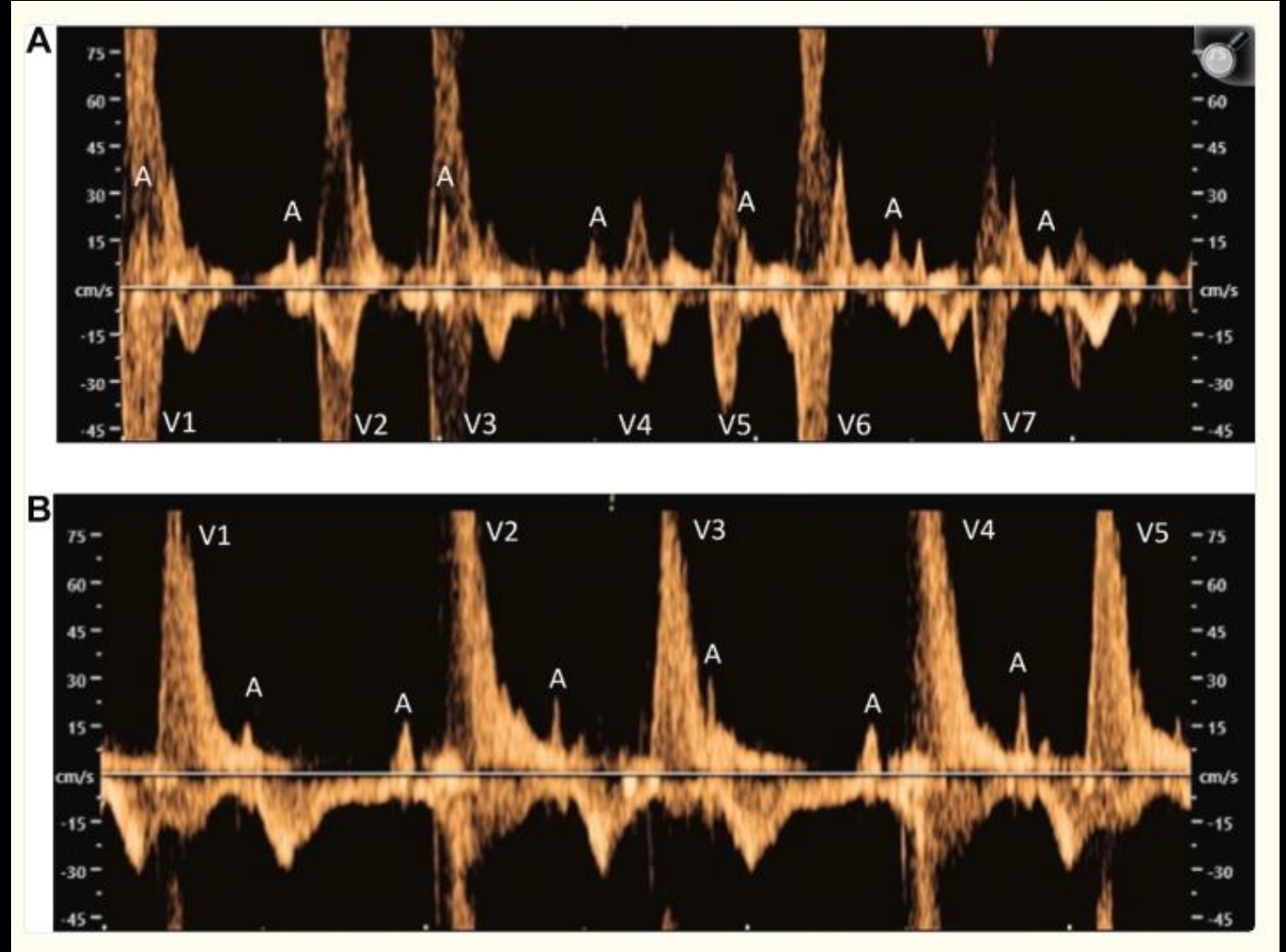


Case #3

Simultaneous fetal tachycardia 170-200 bpm and fetal bradycardia 50-107 bpm

Differential diagnoses:

- SSA antibody-mediated
- Long QT syndrome (KCNH2 or SCN5A)



Putra et al, 2023

Genetic Testing Results

Given clear phenotypes → arrhythmia panel:

#. Pathogenic de novo *KCNH2* c.1898A>G p.Asn633Ser – LQTS type II

Maternal-fetal pharmacogenomic testing were performed:

Selected Maternal and Fetal Pharmacogenomic Results

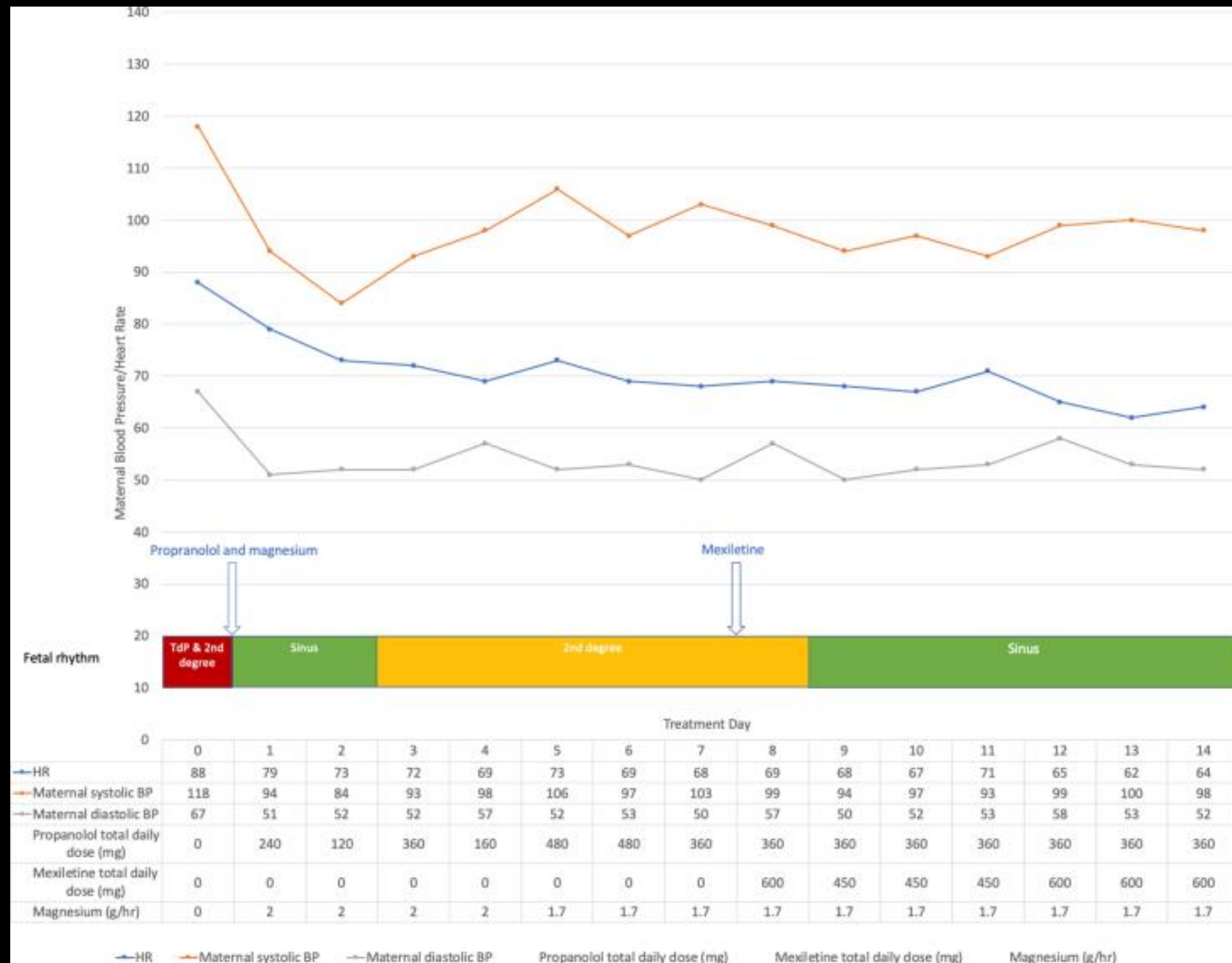
Gene	Maternal Genotype/Phenotype	Fetal Genotype/Phenotype
<i>CYP1A2</i>	*1A/*1F rapid metabolizer	Not tested
<i>CYP2B6</i>	*1/*6 intermediate metabolizer	*1/*1 normal metabolizer
<i>CYP2C9</i>	*1/*1 normal metabolizer	*1/*1 normal metabolizer
<i>CYP2C19</i>	*2/*2 poor metabolizer	*2/*2 poor metabolizer
<i>CYP2D6</i>	*4/*6 poor metabolizer	*4/*6 poor metabolizer
<i>CYP3A4</i>	*1/*22 intermediate metabolizer	rs2740574 TT normal metabolizer
<i>UGT1A1</i>	*1/*28 intermediate metabolizer	*80/*80 poor metabolizer

Case #3

- IV magnesium sulfate was started
- Within 24-hour sinus rhythm was restored
- Propranolol 40mg Q6H and mexiletine 150 mg Q8H were started
- CYP2D6 is a primary pathway for propranolol and mexiletine metabolism
- Poor metabolizer = clear medications slower = lower dose required

Case #3

- Maternal and fetal response:
- Maternal rapid response
 - Maternal side effects
 - Fetal arrhythmia resolutions



Outcome Case #3

- Elective cesarean delivery at 37 weeks
- Had brief run of Torsades immediately resolved with lidocaine and magnesium
- Successfully treated with propranolol



Thank you

Nash Putra, MD

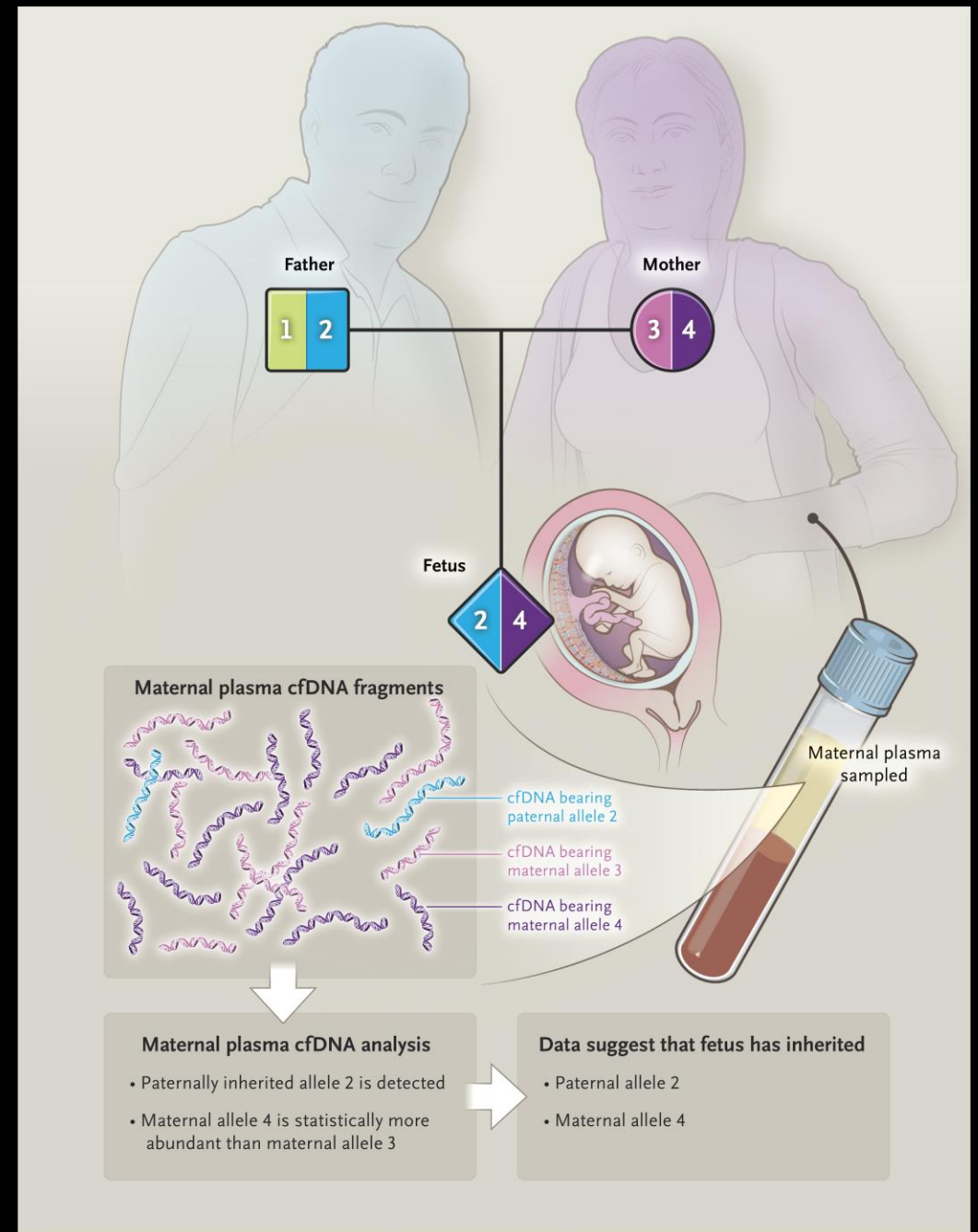
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Rate of CPM by chromosomal aneuploidy

Chromosome	Rate of CPM	Rate of abnormal FTS
Trisomy 21	2%	~77%
Trisomy 18	4%	70-98%
Trisomy 13	22%	70-100%
Monosomy X	59%	Unclear, large ascertainment bias

Screening Options

Many flavors of NIPT



Data on performance of AD sgNIPT

- Analytically easier, since typically absent from maternal genome
- Covers limited conditions:
 - Some skeletal dysplasia
 - Rasopathies
 - Rett, CHARGE, Cornelia de Lange
- Good if declines diagnostic testing in US abnormalities
- Performance: reaches 100% sensitivity and specificity for de novo and paternal variants (Zhang 2019, Mohan 2022)

Data on performance of AR sgNIPT

- 7,538 subjects were carriers and had reflex sgNIPT for CFTR, SMN1, and HBA, HBB.
- Outcomes from 528 cases (~7%)
 - Sensitivity of 96.0% (95% CI: 79.65%-99.90%)
 - Specificity of 95.2% (95% CI: 92.98%-96.92%)
 - Average PPV of 50.0% (95% CI: 35.23%-64.77%)
 - Average NPV of 99.8% (95% CI: 98.84%-99.99%)
- Exclusion:
 - Known carrier couples
 - Multiple gestations