Decoding Prenatal Genetics: Counseling, Testing, and Screening Options

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Disclosures

- Billion to One

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Outline

- Aneuploidy screening: why is it important?
- Methods of screening
- Ultrasound for fetal assessment
- Carrier screening
- Referral to reproductive genetics

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Aneuploidy Screening: What and Why?

- **Screening test:** a strategy used to look for as-yet unrecognized conditions or risk markers.
  - First check, quad screen, NIPT
  - Tells a mother the **likelihood** that the fetus has an extra copy of chromosome 13, 18, 21, or sex-chromosome issues
- **Diagnostic test:** a strategy used to determine if a condition is present or not.
  - Chorionic villus sampling or amniocentesis
  - Fetal DNA extracted through the above sampling methods is directly evaluated to determine the fetal genetic makeup

ACOG & SMFM. Practice Bulletin No. 163 "Screening for Fetal Aneuploidy. May 2016.

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Why is it offered?

- Anticipatory guidance for a parent
- Impacts pregnancy management
- Aligns goals of care for parents, obstetricians, and neonatal care providers
- Opportunity to provide multidisciplinary support and information

ACOG & SMFM. Practice Bulletin No. 163 "Screening for Fetal Aneuploidy. May 2016.

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What are we screening for?

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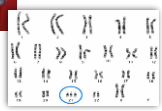
Down Syndrome (Trisomy 21)

- Affects 1 in 700 live births
- Characteristic facial features (flat face, broad nasal bridge, upslanting palpebral fissures, low set ears)
- Increased chance of heart defect or problems with the bowel
- Mild to moderate intellectual disability
- Increased lifetime risk for leukemia and Alzheimer disease



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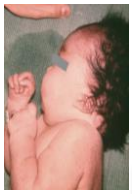
Trisomy 18

- **Affects 1 in 5,000 live births**
- ***Almost always life limiting***
- **Small head and jaw**
- **Low-set ears**
- ***Profound* intellectual disability**
- **Almost all have significant heart defects**
- **Characteristic clenching of the hands**
- **Cleft lip/palate, spina bifida may or may not be present**
- **"Rocker-bottom" feet**
- **Significant kidney problems**



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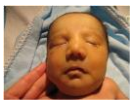
Trisomy 13

- Associated with profound intellectual disability, polydactyly (extra fingers), holoprosencephaly, midline cleft lip/palate
- Close-set eyes, small jaw
- Almost always life limiting



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47, XXX

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Klinefelter Syndrome: 47, XXY

- 1 in 650 male births
- Tall stature
- Increased risk for developmental delays
- Speech-language disorders
- Social-emotional difficulties
- Males with more than one X chromosome may need testosterone replacement therapy and have decreased fertility

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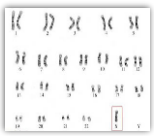
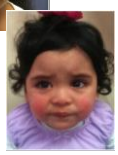
Turner Syndrome: 46, X0

- Essentially normal intelligence,
- short stature, broad chest, webbed neck,
- frequent infertility (underdeveloped ovaries)





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Triploidy

- Three copies of each chromosome
- Not to be confused with TRISOMY (extra copy of only one chromosome)
- Characterized by 3-4 digit syndactyly, severe growth restriction, abnormal ossification of skull
- Other differences dependent on triploidy origin (diandry vs. digyny)

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Importance of Pre and Post Counseling

Positive Screen

Negative Screen

ACOG & SMFM. Practice Bulletin No. 163 "Screening for Fetal Aneuploidy. May 2016.

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Goals of Prenatal Screening & Diagnosis

ACOG & SMFM. Practice Bulletin No. 226"Screening for Fetal Chromosome Abnormalities. Oct 2020.

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Options for screening

- First-trimester screening
- Quad Screen
- Cell-free DNA screening
- Ultrasound alone

ACOG & SMFM. Practice Bulletin No. 226"Screening for Fetal Chromosome Abnormalities. Oct 2020.

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Cell-free DNA Screening

- Evaluates short segments of DNA from the pregnancy in maternal blood
- 5-10% of cell-free DNA in maternal blood is placental
- >10 weeks gestation
- Entire genome of pregnancy is represented in short cfDNA fragments in maternal plasma
- Can be used for: fetal Rh status, sex chromosome evaluation, zygosity, certain heritable conditions (SNP-based testing)

Gil MM et. al Analysis of cell-free DNA in maternal blood in screening for fetal aneuploidies: updated meta analysis. Ultrasound Obstet Gynecol 2015.
Bianchi DW et a.. Genome wide fetal aneuploidy detection by maternal plasma DNA seqeuencing (MELISSA study group). Obstet Gynecol 2012
Norton ME et al. Non-invasive chromosomal evaluation (NICE) study: Am J Obstet Gynecol 2012.

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Accuracy of Screening

Screening Test	Gestational Age (Weeks)	Detection Rate for Trisomy 21 (%)	Screen Positive Rate (%)
First trimester	10-13 6/7	82-87	5
Quad	15-22	81	5
Cell-free DNA	>10	99	0.5
NT alone	10-13 6/7	64-70	5

Bianchi DW et al, Genome-wide fetal aneuploidy detection by maternal plasma DNA sequencing (MELISSA study group). Obstetr Gyencol 2012.
Palomaki et. al DNA sequencing of maternal pasma to detect Down Syndrome: an international clinical validation study: Genetic Med 2011.

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NIPS test performance

	(Total N)	Detection Rate	False Positive Rate
Trisomy 21	(1963)	99.7% (95% CI, 99.1-99.9%)	0.04% (95% CI, 0.02-0.07%)
Trisomy 18	(563)	97.9% (95% CI, 94.9-99.1%)	0.04% (95% CI, 0.03-0.07%)
Trisomy 13	(119)	99.0% (95% CI, 65.8-100%)	0.04% (95% CI, 0.02-0.07%)
Monosomy X	(36)	95.8% (95% CI, 70.3-99.5%)	0.14% (95% CI, 0.05-0.38%)
XXX, XXY, XYY	(17)	93.0% (95% CI, 85.8-97.8%)	0.14% (95% CI, 0.06-0.24%)

Gil et al. Ultrasound Obstet Gynecol. 2017;50:302-314
Slide Courtesy: Emily Hardisty, MS CGC

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Positive Predictive Value

- Predictive Value (PV) is the likelihood that an individual with a negative or positive test result truly does not or does have the disease in question.
- PV is dependent on the PREVALENCE of a condition in a certain population.

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Implications of positive/ abnormal NIPS results

Abnormal NIPS	25 at delivery	35 at delivery	40 at delivery
Chance of Down syndrome	71%	89%	97%
Chance there is **not** Down syndrome	29%	11%	3%

Slide Courtesy: Emily Hardisty, MS CGC

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Implications of positive/ abnormal NIPS results

Abnormal NIPS	25 at delivery	35 at delivery	40 at delivery
Chance of Trisomy 13	20%	49%	78%
Chance there is **not** Trisomy 13	80%	51%	22%

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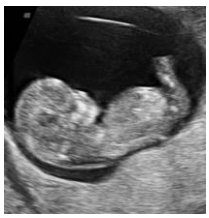
First trimester ultrasound in the setting of cell-free DNA

A nuchal measurement *for aneuploidy risk* is **NOT NECESSARY** at the time of cell-free DNA screening in the first trimester (ACOG, SMFM).

However, **AN ULTRASOUND** is useful to confirm viability, number of fetuses, assign gestational age, and if present, can identify some major fetal anomalies that may **not** be detected by cell free DNA.



Cell-free DNA screening for fetal aneuploidy. Committee Opinion No. 640. ACOG 2015.

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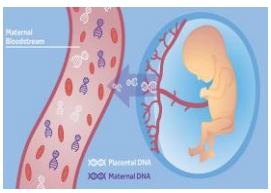
Cell-free DNA screening

False positives
- Placental mosaicism
- Maternal aneuploidy
- Maternal cancer

Low fetal fraction



Taylor-Phillips S et al. Accuracy of non-invasive prenatal testing using cell-free DNA for detection of Down, Edwards, and Patau syndromes: a systematic review and meta-analysis. BMJ Open 2016.
SMFM Statement: Maternal serum cell-free DNA screening in low risk women. 2014.

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Management after failure due to low fetal fraction

All Agree	• Genetic counseling by a genetics professional
AMG[1]	• Offer diagnostic testing
ACOG[2]	• Offer comprehensive ultrasound • Offer diagnostic testing
2015 SMFM Consult Series[3]	• Offer diagnostic testing • Choice to reattempt NIPS screening may depend on gestational age, other maternal factors

1. Gregg AR, et al. *Genet Med.* 2016;18:1056-1065. 2. ACOG Practice Bulletin. *Obstet Gynecol.* 2016;127:e123-137. 3. SMFM. *Am J Obstet Gynecol.* 2015; 212:711-716.
2. Slide Courtesy Emily Hardisty, MS CGC

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Summary of NIPS

- NIPS is currently the most sensitive and specific way of offering screening for trisomy 13, 18, 21, and sex-chromosome aneuploidy
- Predictive value of screening results are dependent on the prevalence
- Low fetal fraction and complex results are often best reviewed with genetic counseling or obstetric provide that can offer prenatal diagnostic services

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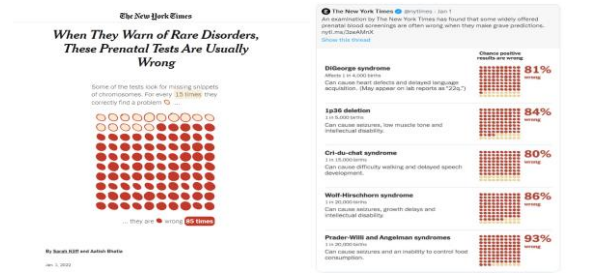

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American College of Medical Genetics

- Recommends against screening for rare autosomal aneuploidies.
- Copy number variants – Inform patients available, increase false-positive and false negative, states laboratory requirements not yet met

American College of Obstetrics & Gynecology

- Recommends against screening for rare autosomal aneuploidies
- Recommends against screening for Copy Number Variants

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Ultrasound

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Second trimester ultrasonography

- For women under 35, ultrasound is the ***least*** effective screening tool for aneuploidy (detection rate of Down Syndrome is 50%).
- Ultrasound is used in adjunct with aneuploidy screening.
- Can detect fetal structural abnormalities.
- Ultrasound alone is NOT a genetic screen or test.

Egan JF et al Role of ultrasound for Down syndrome screening in advanced maternal age. AJOG 2001.
Vintzileos AM et al. Down syndrome risk estimation after normal genetic sonography. AJOG 2002.

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Level II Ultrasound

- Level II ultrasound is a detailed survey of fetal anatomy
- Can detect structural anomalies
- When anomalies are present, there is an increased risk of cytogenetic abnormality

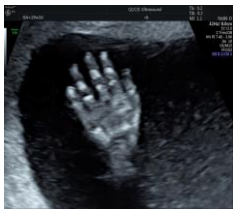

Image Courtesy QDOS Ultrasound

Reimers RM et al. When ultrasound anomalies are present: An estimation of the frequency of chromosome abnormalities not detected by cell free DNA aneuploidy screens. Prenatal Diagnosis 2018.

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Does NIPS rule out spina bifida?

- NIPS does NOT specifically screen for spina bifida and does not provide serum marker (alpha feto-protein, AFP) in its results.
- So… do we need a mid-trimester AFP?
- NO! Advanced ultrasound is good enough to screen for an open neural tube defect!

ACOG Committee Opinion Number 187: Neural Tube Defects.

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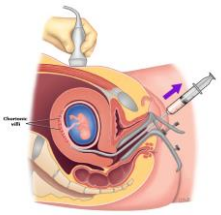
Prenatal Diagnosis: Genetic Counseling and Maternal Fetal Medicine Services



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Carrier Screening

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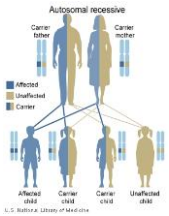
Why Perform Carrier Screening

- Certain autosomal recessive conditions have HIGH carrier frequencies in the general population (pan-ethnic)
- Allows for risk stratification for the pregnancy
- Informs neonatal and pregnancy care
- Provides information for reproductive planning for parents



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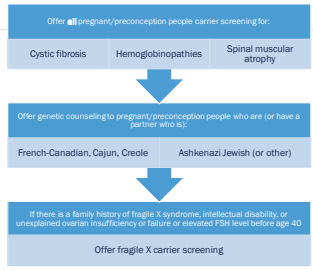
Current Recommendations

2017 ACOG carrier screening guidelines (Numbers 690 and 691)



Slide Courtesy: Emily Hardisty, MS CGC

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How common are these conditions?

- 1 in 9 pregnant/preconception people are carrier of serious genetic disorders
- 80% of affected babies are born to couples with no family history

> Carrier screening should be offered to pregnant women and women considering pregnancy, regardless of ethnicity and family history.
>
> The American College of Obstetricians and Gynecologists (ACOG)

	White	African-American	Hispanic	Asian
Cystic fibrosis	1/2,500	1/15,000	1/13,500	1/35,000
Spinal muscular atrophy	1/ 5,000	1/17,400	1/54,000	1/10,000
Hemoglobinopathies	Mediterranean highest risk: 1/2,500 beta thal 1/3,600 alpha thal	1/300 (Sickle cell) Also beta/alpha thal trait common	1/3,600 beta thal Sickle cell also more common	1/1,600 alpha thal 1/10,000 beta thal

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Carrier Screening

- Carrier screening is **optional**
- Patient education & informed decision-making is essential
- Most tests detect a majority, **but not all carriers** — Especially in the setting of a family history, e.g. of cystic fibrosis
- Genetic counseling is available and recommended for carriers and carrier couples and patients with a family history

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Therapeutic options emerging

- **SMA has effective treatments, but the only way to get a diagnosis early enough is through prenatal screening**
- **With the advancements in gene editing, saving cord blood stem cells (the most potent form of hematopoietic stem cells) of the affected babies may be the source for cure in the future**
- **In-utero stem cell transplant clinical trials are available for selected condition**
- **Time to coordinate your care (change your insurance, find a care team, plan financially, etc.) is more valuable than you think**
- **Families may alter pregnancy management once they know that their pregnancy is affected**

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Genetic Counseling

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Reasons to refer for reproductive genetic counseling

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- Abnormal or failed NIPS/AFP/Quad.
- Abnormal ultrasound finding.
- Coordination of NIPS in twin pregnancies, vanishing twins, or after IVF with PGT.
- Prior pregnancy with a genetic condition or birth defect.
- Patient or partner known carrier of a genetic condition.
- Family history of ID/autism/genetic condition.
- Patient interest in discussing screening/testing options, expanded carrier screening, or maternal age ≥ 35 at delivery.

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Emerging technologies

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Cutting edge technologies

- Carrier screening with reflex single-gene NIPS
- Single-gene NIPS for *de novo* conditions (conditions that tend to happen in the absence of a family history)
- Testing fetal trophoblast cells circulating in maternal blood for aneuploidy and chromosome deletions

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Meet our team

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MFM-Genetics Fellow

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Sample Cases

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NIPS/NIPT sample failures

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INVITAE

INVITAE NON-INVASIVE PRENATAL SCREENING

SAMPLE FAILURE

Results are unavailable: Specimen does not meet quality metrics

Next Steps

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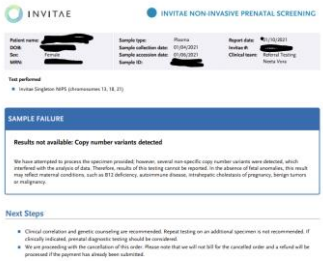
INVITAE

INVITAE NON-INVASIVE PRENATAL SCREENING

SAMPLE FAILURE

Results not available: Copy number variants detected

Next Steps

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Sample failure

- Regardless of the comments on the laboratory report, we recommend the following follow-up after a sample failure:
  - Do not redraw in the office.
  - Refer patient for ASAP genetic counseling to discuss the following options:
    - Redraw (possibly through a different laboratory)
    - Diagnostic testing via CVS or amniocentesis
    - Screening using a different method
    - Anatomy ultrasound
    - In rare cases – maternal health evaluation may be indicated

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Family history – how to handle

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Family history of cystic fibrosis

- Order carrier screening for CF, SMA, hemoglobinopathies?
- Offer expanded carrier screening?
- Refer for genetic counseling?

A 25 year old patient of Hispanic ancestry presents to clinic at 12 weeks in her first pregnancy.

She reports that she has a brother with cystic fibrosis with lung disease and digestive disease

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Family history of cystic fibrosis

- Patient goes to see the genetic counselor
- Cystic fibrosis testing often looks for a set number of pathogenic variants in the gene (the most common 32 or 60 is typical).
- Medical records are obtained and the patient's brother has two rare pathogenic variants that would have been missed if you had ordered CF testing in clinic.

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Family history of Down syndrome

- Order quad screen in clinic?
- Order NIPS in clinic?
- Refer for genetic counseling?

A 27 year old patient presents to clinic. She has a 2-year-old with Down syndrome and has had 3 miscarriages.

She expresses interest in knowing if the current pregnancy also has Down syndrome.

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Family history of Down syndrome

- Patient goes to see the genetic counselor.
- Records indicate that the child with Down syndrome has a 14;21 unbalanced translocation.
- The genetic counselor orders testing on the patient and her partner. The patient has a balanced 14;21 translocation.

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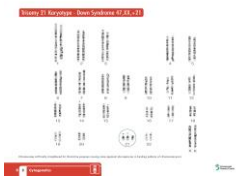
Family history of Down syndrome



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Family history of Down syndrome

- The patient is offered CVS or amniocentesis by the genetic counselor and declines.
- The patient elects to have NIPS, but has had thorough counseling now regarding the chance of recurrence of Down syndrome for both the current pregnancy and future pregnancies.

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