

# Updates on Prenatal Genetic Screening and Testing

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# Disclosure

- No financial relationships to disclose



# Objectives

- 1. Discuss the importance of prenatal testing and screening*
- 2. Describe current prenatal testing and screening options*
- 3. Discuss when confirmatory testing is needed after birth*
- 4. Review when patients should be referred for genetic counseling.*
- 5. Describe the importance of taking a family history*



# Screening versus Testing

- A screening test is used to identify if a baby is more likely to have certain conditions, but cannot make a definitive diagnosis and does not screen for all diseases
- A diagnostic test can often provide a definitive diagnosis
- Even when all the results of diagnostic testing are normal, all pregnancies still have approximately a 3-5% risk of birth defects



# What is prenatal genetic screening or testing testing?

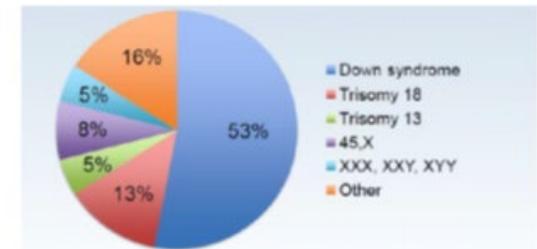
- Prenatal screening for aneuploidy provides an assessment of a woman's risk of carrying a fetus with one of the more common fetal aneuploidies
- Prenatal diagnostic testing evaluates for the presence or absence of abnormalities in chromosome number, deletions and duplications, or specific single gene disorders.
- No one screening test is superior to other screening tests in all test characteristics



# How common are chromosome abnormalities?

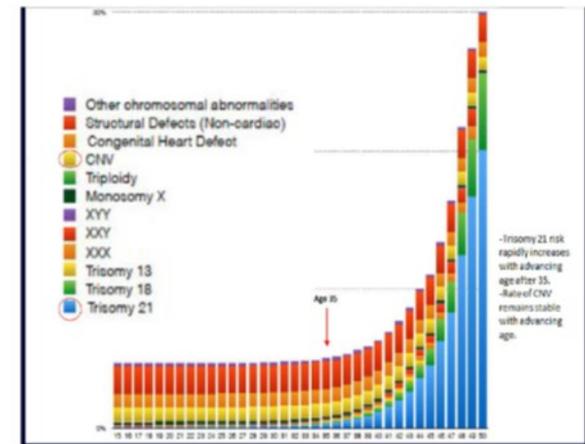
- Chromosome abnormalities occur in 1 in 150 live births
- The incidence of aneuploidy (T21>T18>T13) increases with maternal age, but can affect patients at any age and is not related to race or ethnicity
- In addition, copy number variants (CNV) occur in approximately 0.4% of pregnancies and are unrelated to maternal age
- For patients under age 35, the risk of a CNV is significantly higher than that of common aneuploidies (T13, 18,21)

Figure 1. Prevalence of Aneuploidy



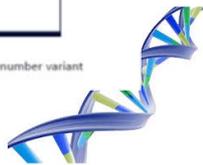
Adapted from Wellesley et al, 2012

Figure 2. Prevalence of Chromosome abnormalities by age



Adapted from Ferreira et al and Wapner et al

CNV = Copy number variant



# Maternal Age Related Risk

## Maternal Age Related Risk for Chromosome Abnormalities

Maternal Age	First Trimester		Second Trimester		Live-birth	
	Down Syndrome	All	Down Syndrome	All	Down Syndrome	All
20	1 in 1152		1 in 1211		1 in 1477	
21	1 in 1125		1 in 1184		1 in 1461	
22	1 in 1110		1 in 1168		1 in 1441	
23	1 in 1090		1 in 1147		1 in 1415	
24	1 in 1064		1 in 1120		1 in 1382	
25	1 in 1032		1 in 1085		1 in 1340	1 in 476
26	1 in 978		1 in 1029		1 in 1287	1 in 476
27	1 in 928		1 in 997		1 in 1221	1 in 455
28	1 in 856		1 in 901		1 in 1141	1 in 435
29	1 in 775		1 in 827		1 in 1047	1 in 417
30	1 in 868		1 in 733		1 in 939	1 in 385
31	1 in 591		1 in 632		1 in 821	1 in 385
32	1 in 494		1 in 536		1 in 696	1 in 323
33	1 in 401		1 in 435		1 in 572	1 in 286
34	1 in 315		1 in 346		1 in 456	1 in 244
35	1 in 240	1 in 114	1 in 265	1 in 141	1 in 353	1 in 179
36	1 in 179	1 in 87	1 in 197	1 in 111	1 in 267	1 in 149
37	1 in 131	1 in 66	1 in 147	1 in 88	1 in 199	1 in 123
38	1 in 96	1 in 51	1 in 108	1 in 70	1 in 148	1 in 105
39	1 in 71	1 in 38	1 in 80	1 in 56	1 in 111	1 in 81
40	1 in 53	1 in 28	1 in 60	1 in 44	1 in 85	1 in 63
41	1 in 41	1 in 22	1 in 47	1 in 35	1 in 67	1 in 49
42	1 in 32	1 in 17	1 in 38	1 in 28	1 in 54	1 in 39
43	1 in 27	1 in 13	1 in 31	1 in 22	1 in 45	1 in 39
44	1 in 22	1 in 10	1 in 26	1 in 18	1 in 39	1 in 31
45	1 in 19	1 in 8	1 in 23	1 in 14	1 in 35	1 in 24



# Spontaneous Pregnancy Loss

- Risk of spontaneous loss between 6-12w in women < 35 is 9-12%
- Risk approaches 50% in women >40 years of age
- >50% of early losses due to chromosome abnormalities
  - Monosomy X, Polyploidy, Trisomy 16, 13, 18, 21, and 22



# Common Chromosome Conditions

**Table 1. Characteristics of Common Chromosome Conditions<sup>7</sup>**

CONDITION	CLINICAL FEATURES	PREVALENCE	LIVE BIRTH RATE	PROGNOSIS
<b>TRISOMY 21 (DOWN SYNDROME)</b>	Cardiac defects, duodenal atresia, mild to moderate ID, thyroid dysfunction, hearing loss, inc risk for leukemia, early onset dementia	-1 in 294 -50-75% risk of miscarriage in first and second trimester.	1 in 700	-80% of children reach 60 years of age or older. -20-25% mortality in 1 <sup>st</sup> year of life secondary to CHD.
<b>TRISOMY 18 (EDWARD SYNDROME)</b>	Cardiac defects, renal anomalies, severe ID, FGR, omphalocele, CNS anomalies, rocker bottom feet, micrognathia, low-set ears	1 in 1111 (at age 35)	1 in 3000	<10 % of children reach 1 year of age.
<b>TRISOMY 13 (PATAU SYNDROME)</b>	Cardiac defects, renal anomalies, cleft lip/palate, holoprosencephaly, microcephaly, omphalocele, severe ID, deafness, seizures	1 in 2500 (at age 35)	1 in 5000	< 10% of children reach 1 year of age.
<b>MONOSOMY X (TURNER SYNDROME)</b>	Cystic hygroma, Aortic coarctation, short stature, ovarian failure, webbed neck, impaired glucose tolerance, thyroid disease and hearing loss, learning disabilities	-1-2% of all conceptuses -99% result in first trimester miscarriage -does not vary with age.	1 in 2500	-Shorter than average life expectancy (~13 years) -Most common cause of death CVD.
<b>47,XXY (KLINEFELTER SYNDROME)</b>	Males with tall stature, small testes, gynecomastia, and azoospermia, learning disabilities	1 in 500 to 1 in 1000	1 in 500	Average life expectancy



# Society Recommendations

- Given the prevalence of chromosomal abnormalities, ACOG recommends that all women be offered the option of aneuploidy screening or diagnostic testing for fetal genetic disorders, regardless of maternal age.
- Patients should be aware that screening is most sensitive for Down syndrome and the detection rate for other aneuploidies may be lower.
- The only method to accurately evaluate for chromosomal abnormalities is via diagnostic testing.
- When a screening strategy is chosen, only one screening test should be performed.
- **Patients should also be informed that making a definitive pregnancy decision based on the results of screening test alone (serum or NIPT) is not recommended.**
- Testing for chromosomal abnormalities should be an informed patient choice based on a variety of factors including access to accurate information, the patient's clinical context, health care resources, values, interests and goals.
- After review and discussion, every patient has the right to **pursue or decline** prenatal genetic screening and diagnostic testing.



# What testing options are available?

	DIAGNOSTIC TESTING <sup>1</sup>		SCREENING TESTS <sup>2,3</sup>		
	CVS	Amnio	Combined Screen	Quad Screen	NIPT <sup>4</sup>
TIMING	11-13 week 6 days (may be performed later in certain cases)	≥ 15 weeks	10-14 weeks	15-22 weeks	≥10 weeks
PROCEDURE	Invasive	Invasive	US and Maternal blood	Maternal Blood	Maternal Blood
RISK	0.1-0.3% miscarriage	0.1% miscarriage	None	None	None
DETECTION RATE	>99% for aneuploidy	>99% for aneuploidy	82-87% T21	81% T21	>99% T21
FPR	<2%	<1%	5%	5%	<0.5-4%
PPV	N/A	N/A	2-4%	2-4%	>/= 35 80%/ < 35 50%
TAT	2 weeks	2 weeks	1 week	1 week	1-2 weeks
CONDITIONS EVALUATED	-Fetal aneuploidy -CNVs -Single gene disorders	-Fetal aneuploidy -CNVs -Single gene disorders -Viral studies -Open fetal defects (AFAFP)	-Trisomy 18, 21, +/- 13 -Fetal anomalies (esp cardiac with inc NT)	-Trisomy 18, 21, +/- 13 -Open fetal defects (MSAFP)	-Trisomy 13, 18, 21 -Sex chromosomes
INCIDENTAL FINDINGS/ ASSOCIATIONS	-Secondary findings -Variants of uncertain significance (1-2%) -Non-paternity -Consanguinity	-Secondary findings -Variants of uncertain significance (1-2%) -Non-paternity -Consanguinity	-Adverse obstetric outcomes (Pre-e, PTB, FGR)	-Adverse obstetric outcomes (Pre-e, PTB, FGR)	-Maternal genetic disorders -Maternal chromosome abnormality -Maternal malignancy/tumor

1. May include Karyotype, chromosomal microarray, single gene panel, WES/WGS, enzyme studies
2. Risk assessment may be adjusted based on the presence or absence of ultrasound findings when using combined or quad screen.
3. This is not an exhaustive list of screening options only those used most frequently in our practices.
4. PPV higher than traditional screening, but highly dependent on gestational age.  
Younger patients should be informed that although cffDNA is an accurate screening test for T21, they are at higher risk for CNV.



# Additional Screening Recommendations

## Ultrasound

- **First trimester • 11-14 weeks**
  - May include NT measurement, Nasal bone
  - Enlarged NT associated with aneuploidy (T21, T18, 45X), genetic syndromes (Noonan), skeletal dysplasia and congenital heart defects (CHD) NT alone has a 70% detection rate for T21
- **Second trimester • 18-22 weeks**
  - Offer to all patients regardless of testing choices
  - Offer maternal serum AFP if not previously performed
  - Evaluation of structural defects
  - Only 27% of fetuses with T21 have recognizable major structural abnormality by ultrasound.
  - The sensitivity of ultrasound in detecting fetal anomalies varies by center expertise and organ system ranging from 20-90%.

## Multiple Gestation

- **Twins:**
  - No method is as accurate as it is for singletons.
  - Traditional screening in twin pregnancies: Maternal age and nuchal translucency (with or without biochemistry) detects up to 80% of Down syndrome at a 5% false positive rate.
  - cfDNA-based screening for common trisomies in twins provides higher positive predictive values among twin pregnancies compared with traditional serum and nuchal translucency based screening in twins, but are associated with test failures.
  - Interpretation of the cfDNA test results could differ depending on test methodology, fetal fraction and chorionicity/zygosity.
- **Triplets and higher order multiples**
  - Screening options for triplet pregnancies are lacking and cfDNA may be a potential option. There are currently few if any observed data to determine detection rates. Failure rates up to 20% have been reported.



# Next Steps if Screen Positive

- In patients with a screen positive and abnormal ultrasound findings invasive testing is recommended
- Cell-free fetal DNA screening may be used as a follow up but patients should be advised that this may delay definitive diagnosis
- If invasive testing is declined postnatal examination and testing is recommended
- Residual risk of a chromosomal abnormality with a normal cell-free fetal DNA screening after abnormal traditional screening is 2%



# Invasive Testing

- Who should be offered invasive diagnostic testing for aneuploidy?
  - Everyone, regardless of maternal age.
  - Must discuss risks vs benefits
  - All patients with abnormal screening result, abnormal ultrasound finding, or positive history
  - When trisomy 21, 18, and 13 are the only aneuploidies screened for, ~50% of cytogenetic abnormalities routinely identified by amniocentesis will not be detected
- When patients <35 years or >35 years are considered separately, 75 and 43% of cytogenetic abnormalities will be missed



# Chorionic Villus Sampling (CVS)

- Performed between 10-13 weeks
- Indications same as for amniocentesis
  - AFP testing cannot be performed\*
- Miscarriage risk ~1/300-500
- Mosaicism seen in 1-2%
  - 20% are true mosaics
  - 80% are confined placental mosaicism
- Primary advantage is timing
- Failure rate is <0.5%



# Amniocentesis

- Performed after 15 weeks
- Miscarriage risk  $\sim 1/300$
- AFP included
  - Followed by acetylcholinesterase (AChE) confirmatory testing on positive results
- Failure rate is 0.1%



# Who needs a genetic counseling referral?

- Advanced maternal age/Advanced paternal age
- Abnormal screening test result
- Fetal structural anomaly on prenatal ultrasound
- Family history of a known or suspected genetic disorder
- Known carrier of a genetic condition
- Parental history of genetic disorder
- Known teratogenic exposure
- Consanguinity (blood relationships of parents, first cousins or closer)
- Recurrent pregnancy loss (2 or more first trimester losses)
- Prior child with chromosome abnormality or genetic disorder
- History of stillbirth or fetal/neonatal loss with structural anomalies
- Patient request for additional information regarding testing options



# Why is taking a family history important?

- An accurate family history is a method to recognize genetic disorders and susceptibilities that may pose risks for future health problems.
- The family history is the initial step before discussing genetic testing with your patient.
- The use of a family history screening tool has been shown to increase the likelihood of detecting a patient at high risk of developing an inherited medical condition by 20% compared to medical record review alone.
- **What is the best way to record a family history and what types of information should be included?**
  - A common tool used to collect the family history is the family history questionnaire or checklist
  - Having the patient complete the questionnaire at home allows extra time for the patient to contact family members and provide more accurate information.
  - Remind your patient that the family history is a lifetime document that should be transferred to new physicians as they move through the health care system.
  - Remember that the personal nature of this information requires questions to be open ended and non-judgmental.
  - Families that have medical conditions appearing in multiple relatives need to be reassured that no one is to blame when genetic conditions are passed on to future generations.
- **How should the family history be interpreted?**
  - Any positive responses should be followed up to obtain more detail.
  - Positive responses should be referred for genetics services.



# Examples of “red flags” in a family history suggesting a genetic condition

- Family history of a known or suspected genetic condition
- Ethnic predisposition to certain genetic disorders
- Consanguinity
- Several closely related individuals affected with the same or related condition.
- A common disorder with earlier age of onset than typical, especially if it occurs in multiple family members.
- Sudden death in someone who seemed healthy.
- Individual or couple with 2 or more pregnancy losses.
- Medical problems in children of parents who are closely related.
- Within an individual, look for:
  - A medical condition and dysmorphic features
  - Developmental delay with dysmorphic features and/or physical birth anomaly
  - Learning disabilities or behavioral problem
  - Unexplained movement disorders, hypotonia, ataxia
  - Unexplained seizures
  - Congenital/juvenile deafness, blindness or cataracts
  - Disproportionate short stature or proportionate short stature with dysmorphic features
  - Unexplained infertility



# Insurance Coverage for cell-free fetal DNA Screening

- Due to the complexity of coverage guidelines, insurance coverage for prenatal genetic testing and screening may not be guaranteed. Patients are encouraged to contact their insurance company to obtain benefits coverage, so that there are no surprises.



# Take Home Points

- All pregnancies have approximately a 3-5% risk of birth defects
- All women should be offered the option of aneuploidy screening or diagnostic testing for fetal genetic disorders, regardless of maternal age or history
- Every patient has the right to **pursue or decline** prenatal genetic screening and diagnostic testing
- The first step to genetic screening is a thorough history
- Don't hesitate to make genetic referrals



# References

- ACOG PB number 162, Invasive Prenatal Testing for Aneuploidy
- SMFM consult series, number 41
- SMFM Consult series, number 42
- ACOG PB number 226, Screening for fetal chromosome abnormalities
- ACOG PB number 187,
- ACOG CO number 682, Microarrays and Next Generation sequencing technology: The use of advanced genetic diagnostic tools in obstetrics and gynecology
- ACOG CO number 478, Family History as a Risk Assessment Tool
- ACOG CO 693, Counseling about genetic testing and communication of genetic testing results
- Technology Assessment number 11, Genetics and Molecular Diagnostic Testing
- American Medical Association Science, Quality and Public Health Group. Family medical history in disease prevention. November 2004.
- International Society for Prenatal Diagnosis (ISPD) Position Statement: cell free (cf)DNA screening for Down syndrome in multiple pregnancies



# References (cont.)

- Recent advances in genomic testing in perinatal medicine. Peters, et al. *Seminars in perinatology* 39 (2015) 44-54.
- Non-Invasive prenatal testing for aneuploidy: current status and future prospects, Benn, et al
- Meta-analysis for 2<sup>nd</sup> Trimester markers for trisomy 21, Agathokleous, et al FASTER and SURUSS Trial
- Wellesley et al. Rare chromosome abnormalities, prevalence and prenatal diagnosis rates from population-based congenital anomaly registers in Europe
- Alijotas-Reig et al. Current concepts and new trends in the diagnosis and management of recurrent miscarriage. *Obstet Gynecol Surv.* 2013
- Ferreira et al. Frequency of fetal karyotype abnormalities in women undergoing invasive testing in the absence of ultrasound and other high-risk indications.
- Wapner RJ, et al. Chromosomal microarray versus karyotyping for prenatal diagnosis.
- Jones KL, Jones MC, Del Campo M, Smith's Recognizable Patterns of Human Malformation



# References (cont.)

- Norton ME, et al. Cell-free DNA analysis for noninvasive examination of trisomy. *N Engl J Med*. 2015;372(17):1589-1597. Gregg AR, et al. Noninvasive prenatal screening for fetal aneuploidy, 2016 update: a position statement of the American College of Medical Genetics and Genomics. *Genet Med*. 2016;18(10):1056-1065.
- Bianchi DW, et al; CARE Study Group. DNA sequencing versus standard prenatal aneuploidy screening. *N Engl J Med*. 2014 Feb 27;370(9):799-808.
- Benn Paet al. Combined second-trimester biochemical and ultrasound screening for Down syndrome. *Obstet Gynecol*. 2002 Dec;100(6):1168-76.
- Malone FD, et al; First-and Second-Trimester Evaluation of Risk (FASTER) Research Consortium. First-trimester or second-trimester screening, or both, for Down's syndrome. *N Engl J Med*. 2005 Nov 10;353(19):2001-11.
- Hui L, Bianchi DW. Fetal fraction and noninvasive prenatal testing: What clinicians need to know. *Prenat Diagn*. 2020;40(2):155-163.
- Bianchi DW, Chiu RWK. Sequencing of Circulating Cell-free DNA during Pregnancy. *N Engl J Med*. 2018;379(5):464-473.
- Rink BD, Norton ME. Screening for fetal aneuploidy. *Semin Perinatol*. 2016 Feb;40(1):35-43.



# Thank You

- Questions?
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