Obstetrics Genetics Update for the Busy OB/GYN: From Aneuploidy Screening to Fragile X Carrier Testing

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Common Aneuploidies in Liveborn Infants

Disorder	Incidence
Trisomy 21 (Down Syndrome)	1:700
Trisomy 18 (Edward Syndrome)	1:3000
Trisomy 13 (Patau Syndrome)	1:5000
45 X (Turner Syndrome)	1:2500 females
47 XXY (Klinefelter Syndrome)	1:600 males
47 XYY & 47 XXX	1:1500

ACOG Education in Women's Genomic Counseling

Case 1

You're seeing a 30 yo G1 at 10 weeks gestation. You counsel her that the aneuploidy screening option with the highest sensitivity and positive predictive value for T21 is:

A. Nuchal translucency measurement
B. Cell-free DNA screening (cfDNA)
C. Quad screening
D. First trimester serum analyte screening

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Age-Related Aneuploidy Risk

AGE AT TERM	RISK OF TRISOMY 21	RISK OF ANY CHROMOSOMAL ABNORMALITY
15	1:1578	1:454
20	1:1480	1:525
25	1:1340	1:475
30	1:940	1:384
35	1:353	1:178
40	1:85	1:62
45	1:35	1:18

Adapted from ACOG Practice Bulletin 163; Morris et al., Hook et al., Cuckle et al.

Aneuploidy Screening Options - Serum

Test	GA (weeks)	Sensitivity for T21 (%)	Screen Positive Rate (%)*	Advantages	Disadvantages	Methods
Triple screen	15-22	69	5	Open defects & other adverse outcomes	Lower sensitivity; 2nd tri	hcg, AFP, uE3
Quad screen	15-22	81	5	Open defects & other adverse outcomes	Lower sensitivity; 2nd tri	hcg, AFP, uE3, DIA
Serum Integrated	Multiple	88	5	Increased sensitivity	2 samples; no 1st tri results	PAPP-A & Quad screen

* Includes true & false positives

Adapted from ACOG Practice Bulletin 163, Table 2

Aneuploidy Screening Options - NT

Test	GA (weeks)	Sensitivity for T21 (%)	Screen Positive Rate (%)*	Advantages	Disadvantages	Methods
NT only	10-13 6/7	64-70	5	Additional fetal abnl; multiple gestations	Low sensitivity; certification	NT
1st trimester screening	10-13 6/7	82-87	5	Other adverse outcomes	Multiple tests	NT, PAPP-A, hcg
Integrated	Multiple	96	5	Highest sensitivity; open defects	Delayed results; multiple tests	NT, PAPP-A, quad screen
Sequential stepwise	Multiple	95	5	High sensitivity; 1st tri results provided	Multiple tests	NT, PAPP-A, hcg, quad screen
Contingent	Multiple possible	88-94	5	High sensitivity; 1st tri results provided	Complex process; multiple tests	2nd tri testing for intermediate risk

* Includes true & false positives

Adapted from ACOG Practice Bulletin 163, Table 2

Aneuploidy Screening Options – Cell-free DNA

Test	GA (weeks)	Sensitivity for T21 (%)	Screen Positive Rate (%)*	Advantages	Disadvantages	Methods
Cell free fetal DNA (cfDNA)	10+	99 (if result obtained)	0.5	Highest sensitivity; highest PPV	Cost; limited info about other fetal risks	Molecular methods

* Includes true & false positives

Adapted from ACOG Practice Bulletin 163, Table 2

Table 2. Test Performance for Trisomy 21 in the Primary Analysis Cohort, According to Maternal Age and Risk.*

Variable	Standard Screening	Cell-free DNA Testing		
	All Patients (N = 15,841)	All Patients (N = 15,841)	Maternal Age <35 Yr (N = 11,994)	Low Risk (N = 14,957)†
True positive — no.	30	38	19	8
True negative — no.	14,949	15,794	11,969	14,941
False positive — no.	854	9	6	8
False negative — no.	8	0	0	0
Sensitivity (95% CI) — %	78.9 (62.7–90.4)	100 (90.7–100)‡	100 (82.4–100)	100 (63.1–100)
Specificity (95% CI) — %	94.6 (94.2–94.9)	99.9 (99.9–100)§	99.9 (99.9–100)	99.9 (99.9–100)
Positive predictive value (95% CI) — %	3.4 (2.3–4.8)	80.9 (66.7–90.9)§	76.0 (54.9–90.6)	50.0 (24.7–75.3)
Negative predictive value (95% CI) — %	99.9 (99.9–100)	100 (99.9–100)¶	100 (99.9–100)	100 (99.9–100)
Positive likelihood ratio	14.6	1755.9	1995.8	1868.6
Negative likelihood ratio	0.22	0	0	0

Norten, ME et al. NEJM 2015; 372:1589-97

Table 3. Test Performance for Trisomy 18 and Trisomy 13.*

Metric	Trisomy 18		Trisomy 13	
	Standard Screening (N=15,841)	Cell-free DNA Testing (N=15,841)	Standard Screening (N=11,185)	Cell-free DNA Testing (N=11,185)
True positive — no.	8	9	1	2
True negative — no.	15,782	15,830	11,155	11,181
False positive — no.	49	1	28	2
False negative — no.	2	1	1	0
Sensitivity (95% CI) — %	80.0 (44.4–97.5)	90.0 (55.5–99.7)	50.0 (1.2–98.7)	100 (15.8–100)
Specificity (95% CI) — %	99.7 (99.6–99.8)	100 (99.9–100)†	99.7 (99.6–99.8)	100 (99.9–100)†
Positive predictive value (95% CI) — %	14.0 (6.2–25.8)	90.0 (55.5–99.7)†	3.4 (0.1–17.8)	50.0 (6.8–93.2)
Negative predictive value (95% CI) — %	100 (99.9–100)	100 (99.9–100)	100 (99.9–100)	100 (99.9–100)

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Case 2

Your “low risk” patient chooses to pursue cfDNA screening and has a normal result. What do you recommend for subsequent NTD screening?

A. 2nd trimester sono
B. 2nd trimester AFP
C. 2nd trimester sono & AFP
D. None of the above
E. Any of the above

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Case 3

A 24 yo G2P0 at 6 weeks sees you for her 1st prenatal visit. You counsel her that her pregnancy is at highest risk for what type of chromosomal disorder:

A. A sex chromosome aneuploidy
B. Trisomy 21
C. Unbalanced translocation
D. Microdeletion or microduplication

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Common Microdeletion & Duplication Syndromes

Region	Name	Common Features
22q11.21	DiGeorge VCFS	CHD, clefting, ID, immune disorders
5p13	Cri-du-chat	ID, dysmorphia, characteristic cry
17p11.2	Smith-Magenis	ID, dysmorphia, self-mutilation
17p13.3	Miller-Dieker	Lissencephaly, seizures, CHD
15q11q13	Prader-Willi	ID, hypotonia, hyperphagia
7q11.23	Williams-Beuren	CHD, ID, growth deficiency
1p36		ID, CHD, hearing loss
17q21.31		ID, speech disorders, seizures
15q11q13	Angelman	ID, ataxia, seizures

Case 4

A 37 yo G3P0 at 7 weeks initiates care with you after achieving pregnancy via IVF (her eggs). She had aneuploidy screening (PGT-A) & transferred euploid embryos. What do you recommend in pregnancy for aneuploidy screening/testing?

A. Nothing – she already had normal aneuploidy screening
B. Invasive testing only
C. Her preferred screening or testing option (like non-ART pts)
D. Referral to a genetic counselor

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Aneuploidy Testing Confusion

- Erroneous gestational age
- ”Vanishing” twin
- Selective reduction
- Confined placental mosaicism (CPM)
- Maternal malignancy
- Maternal aneuploidy
- Donor eggs

Case 5

You're seeing a 28 yo G2P1 with a di-di twin gestation at 8 weeks. You counsel her that that the aneuploidy screening option best suited to twin pregnancies is:

A. Nuchal translucency measurement (NT)
B. Cell-free DNA screening (cfDNA)
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Case 6

Your patient, a 25 yo G3P2 at 14 weeks gestation had an abnormal NT followed by a normal CVS. You counsel her that her fetus is elevated risk of:

A. Cardiac abnormalities

B. Abdominal wall defects

C. Congenital diaphragmatic hernia

D. All of the above

E. None of the above

Case 6

Your patient, a 25 yo G3P2 at 14 weeks gestation had an abnormal NT followed by a normal CVS. You counsel her that her fetus is elevated risk of:

A. Cardiac abnormalities

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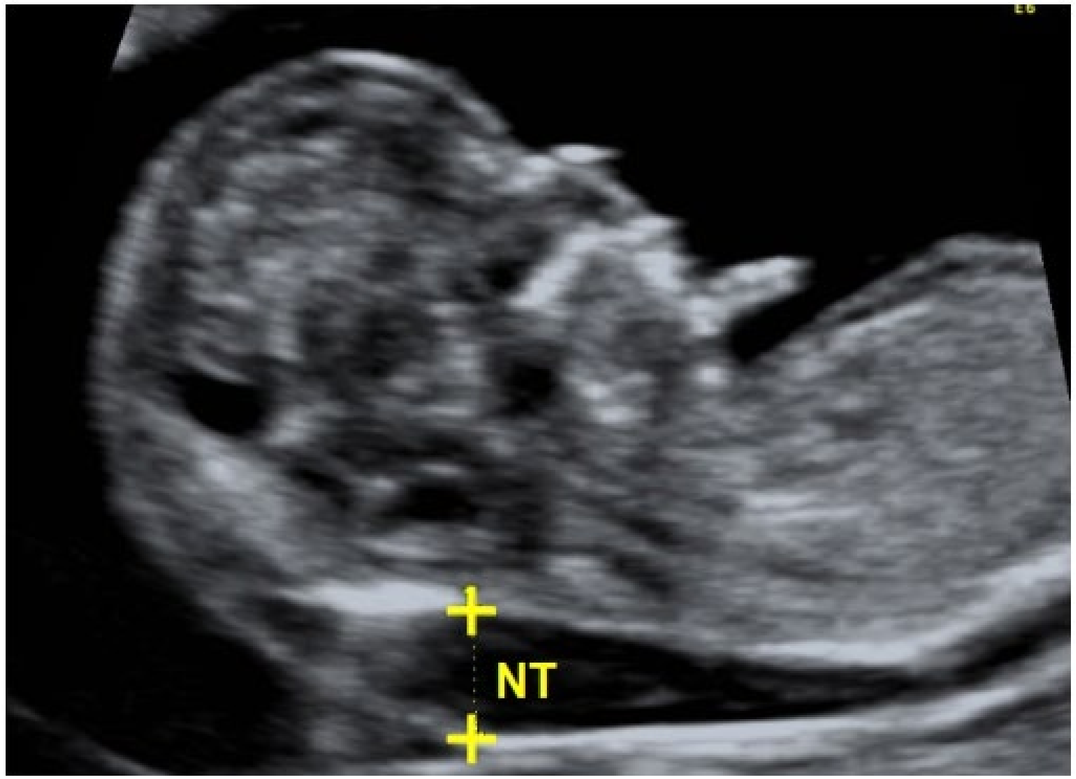
C. Congenital diaphragmatic hernia

D. All of the above

E. None of the above

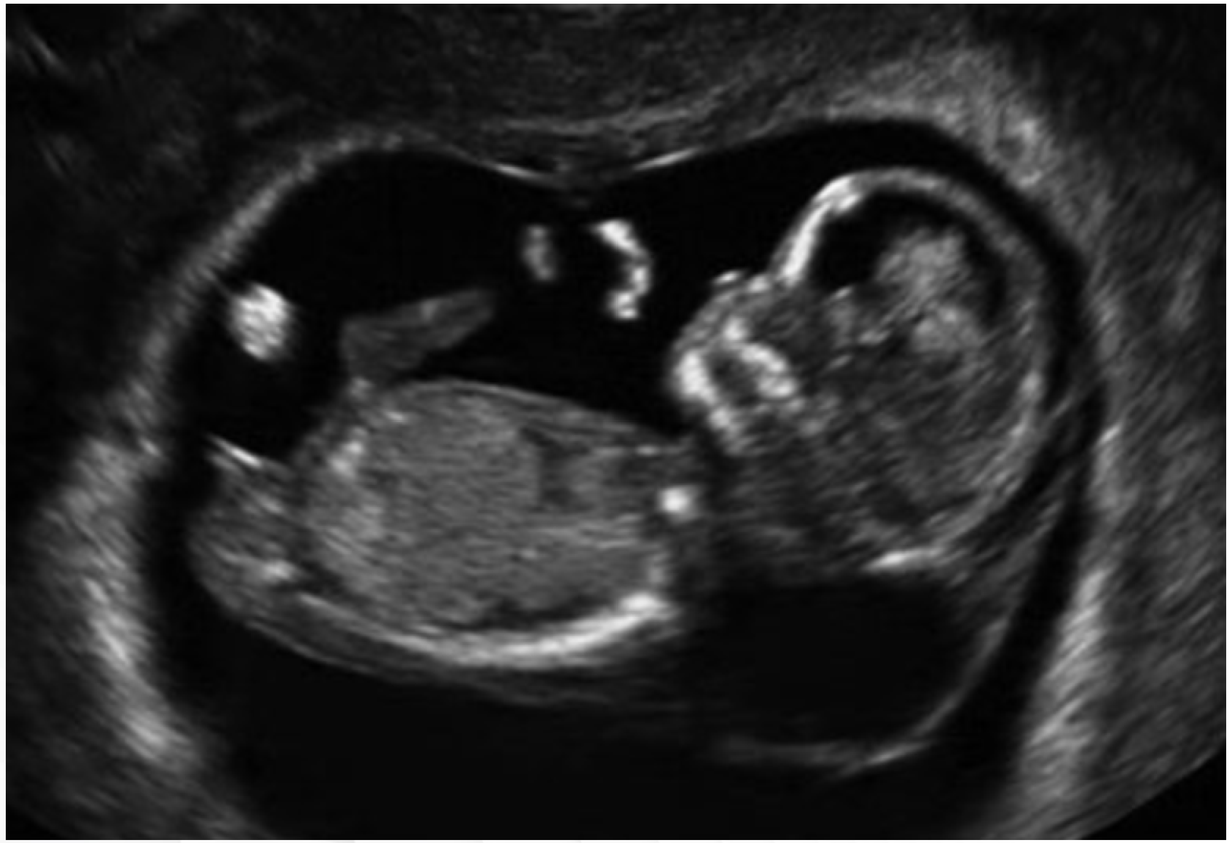
Nuchal Translucency

- Performed by certified sonographer/clinician
- 10-13 6/7 weeks
- Abnormal measurements →
  - Diagnostic testing
  - Targeted ultrasound
  - Fetal echo



www.fetalmedicine.org

Cystic Hygroma



www.sonoworld.com

- 50% aneuploid
  - T21, 45X, T18
- 50% euploid
  - 50% major structural malformation
  - <20% healthy liveborn

Case 7

Your patient, a 37 yo G2P0 at 14 weeks gestation had a cfDNA screen that returned as “no result.” You counsel her that “no result” is associated with:

A. Obesity
B. Aneuploidy
C. Pregnancy dating inaccuracy
D. LMWH use
E. All of the above

Case 7

Your patient, a 37 yo G2P0 at 14 weeks gestation had a cfDNA screen that returned as “no result.” You counsel her that “no result” is associated with:

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Case 8

Your patient, a 36 yo G1 at 18 weeks had an abnormal cfDNA screen followed by a normal amniocentesis. You counsel her that her pregnancy is at elevated risk for:

A. Hypertensive disorders of pregnancy
B. Genetic metabolic disorders
C. Preterm delivery
D. IUGR

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Case 9

According to ACOG, women who have not been previously screened & have a negative family history should be offered carrier testing for what condition(s) during preconception or prenatal care?

A. Cystic fibrosis
B. Fragile X
C. Spinal Muscular Atrophy (SMA)
D. A & C
E. A, B, & C

Case 9

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D. A & C
E. A, B, & C

Carrier Frequencies

Population	Condition	Carrier Frequency
African-American	Sickle Cell Cystic Fibrosis Beta-Thalassemia	1 in 10 1 in 65 1 in 75
Ashkenazi Jewish	Gaucher disease Cystic Fibrosis Tay-Sachs disease Dysautonomia Canavan disease	1 in 15 1 in 25 1 in 30 1 in 32 1 in 40
Asian	Alpha-Thalassemia Beta-Thalassemia	1 in 20 1 in 50
European American	Cystic Fibrosis	1 in 25
French Canadian, Cajun	Tay Sachs disease	1 in 30
Hispanic	Cystic Fibrosis Beta-Thalassemia	1 in 46 1 in 30 - 1 in 50
Mediterranean	Beta-Thalassemia Cystic Fibrosis Sickle Cell	1 in 25 1 in 29 1 in 40

Mayo Clinic

Cystic Fibrosis Carrier Screening

Table 2. Cystic Fibrosis Detection and Carrier Rates Before and After Testing ⇦

Racial or Ethnic Group	Detection Rate* (%)	Individual Carrier Risk Before Testing	Approximate Individual Carrier Risk After Negative Test Result†
Ashkenazi Jewish	94	1/24	1/380
Non-Hispanic white	88	1/25	1/200
Hispanic white	72	1/58	1/200
African American	64	1/61	1/170
Asian American	49	1/94	1/180

*Detection rate data based on use of a 23-mutation panel.

†Bayesian statistics used to calculate approximate carrier risk after a negative test result.

Modified from the American College of Medical Genetics and Genomics. Technical standards and guidelines for *CFTR* mutation testing. American College of Medical Genetics Standards and Guidelines for Clinical Genetics Laboratories. Bethesda (MD): ACMG; 2011. Available at: http://www.acmg.net/docs/CFTR_Mutation_Testing_2011.pdf. Retrieved September 12, 2016.

ACOG Committee Opinion 691 (Reaffirmed 2019)

Spinal Muscular Atrophy Carrier Screening

- Progressive neuromuscular disorder
- Complex genetics
  - AR (SMN1 modified by SMN2*; ASAH1; IGHMBP2)
  - AD
  - X-linked

NIH Genetics Home Reference

Spinal Muscular Atrophy Types

SMA Type	Number of Copies of SMN2	Onset	Incidence per Live Birth among SMA Types	Survival	Characteristics
Type 1 (Werdnig-Hoffman Disease)	Two	Before six months	Approximately 60%	Less than 10% event free* by two years of age	Will never be able to sit without support
Type 2 (Dubowitz Syndrome)	Three or Four	6 – 18 months	Approximately 27%	68% alive at age 25	Will never be able to walk or stand without support
Type 3 (Kugelberg-Welander Disease)	Three or Four	Early childhood to early adulthood (juvenile)	Approximately 13%	Normal	Stand alone and walk but may lose ability to walk in 30s-40s
Type 4	Four to Eight	Adulthood (20s-30s) usually after 30	Uncommon; limited information is available on incidence	Normal	Same as Type 3

www.avexis.com

Case 10

ACOG recommends Fragile X carrier screening for women with:

A. Family history of unexplained intellectual disability
B. Family history of autism
C. Family history of Fragile X
D. Premature ovarian insufficiency
E. All of the above

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Fragile X Expansion

ACOG Committee Opinion 691 (Reaffirmed 2019)

Table 5. Full Mutation Expansion From Maternal Premutation Allele ⇦

Maternal Number of Triplet Repeats (Cytosine–Guanine–Guanine)	Status of Individual	Full Mutation Expansion* (%)
Less than 45	Unaffected	
45–54	Intermediate (also called "gray zone")	
55–59	Premutation	4
60–69	Premutation	5
70–79	Premutation	31
80–89	Premutation	58
90–99	Premutation	80
100–200	Premutation	98
More than 200	Full mutation	100

*The likelihood of expansion to a full mutation also may be affected by other factors, including the presence of AGG interrupters that reduce the risks of expansion.

Modified from Nolin SL, Brown WT, Glicksman A, Houck GE Jr, Gargano AD, Sullivan A, et al. Expansion of the fragile X CGG repeat in females with premutation or intermediate alleles. Am J Hum Genet 2003;72:454–64 with permission from Elsevier and data from Pesso R, Berkenstadt M, Cuckle H, Gak E, Peleg L, Frydman M, et al. Screening for fragile X syndrome in women of reproductive age. Prenat Diagn 2000;20:611–4.

Fragile X-Associated Tremor Ataxia Syndrome (FXTAS)

- Late onset, progressive disorder
- Males more often & severely affected
- Disorder of movement, cognition, & mood
- Women may develop hypothyroidism or pain symptoms before neuro symptoms present

NIH Genetics Home Reference

Case 11

You are seeing a G1 couple for a 1st prenatal visit. The male partner is of Ashkenazi Jewish descent. The female partner is of Japanese descent. There's no family history of genetic disease. What are your recommendations regarding carrier testing for genetic diseases of elevated prevalence in the Jewish population?

A. No testing is indicated since the woman is Japanese
B. Both partners should be offered panel testing
C. The male partner should be offered panel testing
D. No testing is indicated given the negative family history

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Recommended Carrier Screening – Ashkenazi Jewish Patients

ACOG

- Tay Sachs
- Familial dysautonomia
- Canavan disease

ACMG

- Tay Sachs
- Familial dysautonomia
- Canavan disease
- Fanconi anemia C
- Niemann-Pick A
- Bloom syndrome
- Mucolipidosis IV
- Gaucher type 1

Case 12

You are seeing a couple for preconception counseling. Both partners are of Ashkenazi Jewish descent and have family histories that include breast cancer. You counsel them that:

A. Offspring have potential cancer risks similar to parents
B. BRCA1 mutation homozygosity is associated with fetal abnormalities
C. BRCA 2 mutation homozygosity is associated with fetal abnormalities
D. A&B
E. A&C

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Aneuploidy Screening/Diagnosis Principles

- All women should be offered screening & diagnostic testing
  - Potential advantages of information gained
  - Differentiating between screening & diagnosis
  - What is/isn't being screened/tested for

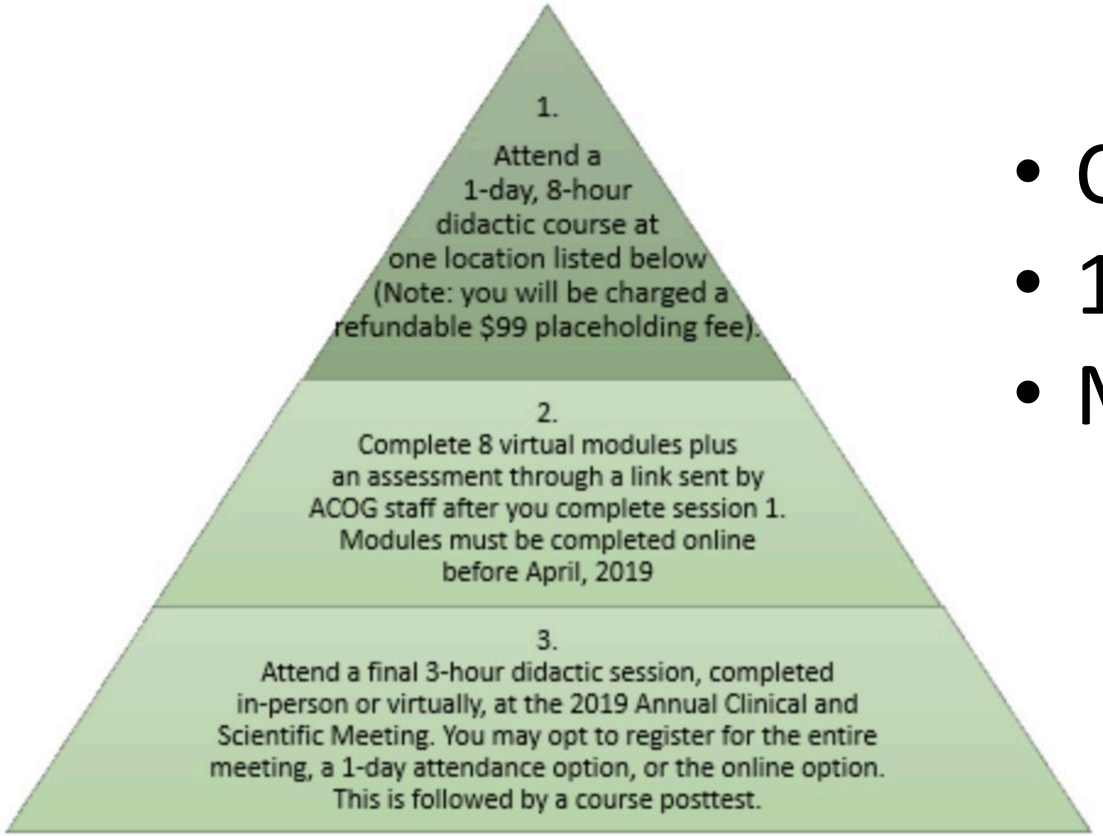
Aneuploidy Screening/Diagnosis Principles

- Pre- & Post-test counseling
  - Pre-test risk
  - Residual risk
  - Unexpected information about parents

Aneuploidy Screening/Diagnosis Principles

- Standard approach to counseling
  - Consider
    - Decision aids
    - Graphic representations
    - Questionnaires
    - Reminder systems/documentation prompts
    - Patient consent forms

ACOG Education in Women's Genomic Counseling



- Certificate
- 18 CME credits
- MOC Part 4 credit

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Questions?

https://www.acog.org/About-ACOG/ACOG-Departments/Genetics

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