OB/GYN Webinar Series 2017-2018

OB/GYN Webinar Series 2017-2018

Special Series: Genetic Testing

Thursday, February 1st, 12pm- 1pm EST

Presented by:

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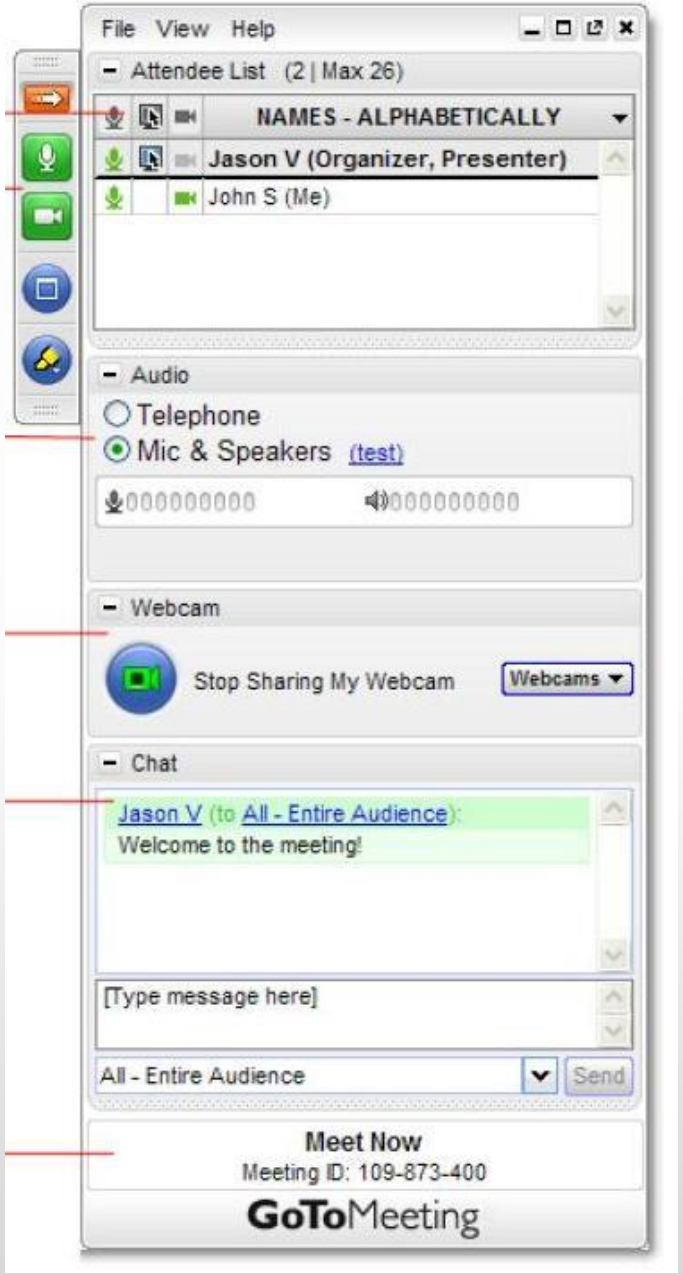
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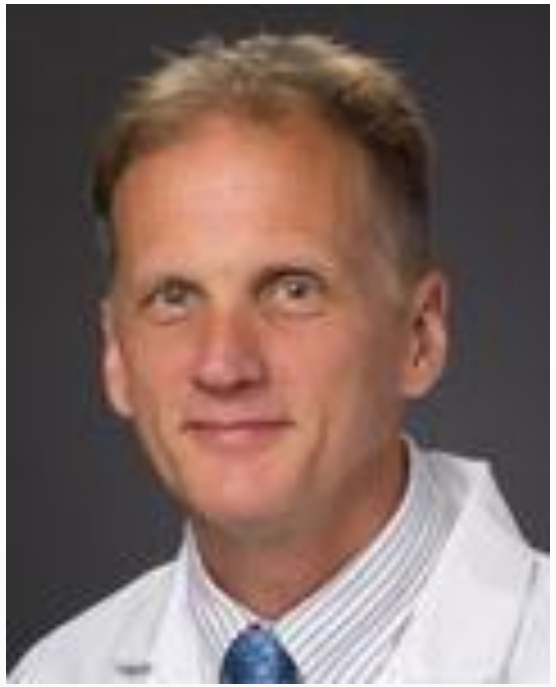
Dr. Stephen Brown, MD

Obstetrics & Gynecology, University of Vermont Medical Center
Associate Professor, University of Vermont Larner College of Medicine



Areas of Expertise:

- Clinical Genetics and Molecular Genetics
- Reproductive Genetics
- Prenatal Diagnoses

OB/GYN VCHIP Webinar Series 2017-2018

Special Series
Webinar 1: DNA-based Aneuploidy Testing

Stephen Brown, MD

Terms for DNA-based Aneuploidy Screening

- NIPT = Non Invasive Prenatal Testing.
- NIPS = Non Invasive Prenatal Screening
- Cff-DNA Testing = cell-free fetal DNA Testing
- There is no good consensus about which term to use.

Educational Goals

- Brief review of where things are with cff-DNA aneuploidy testing
- Discuss need for definitive testing in patients who screen positive.
- Discuss limitations of NIPT.
- Discuss use of DNA-based testing in twins.
- Discuss “expansion” of DNA based testing to sex chromosomes and micro-abnormalities.
- Will NOT discuss use of NIPT in low risk women since this is the subject of a later webinar.

Where are we with NIPT?

- Several competing technologies:
  ”Informaseq” and similar tests through other companies use
  “shotgun sequencing” – simple and effective
  “Harmony” uses targeted sequencing or array – cheap and effective
  “Panorma” uses single nucleotide polymorphism method – allows determination of some triploidies and zygosity of twins
- Very little difference in sensitivity and overall test performance.
- Because of this similarity, companies advertise other stuff

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Systematic Review

Analysis of cell-free DNA in maternal blood in screening for aneuploidies: updated meta-analysis

M. M. Gil, V. Accurti, B. Santacruz, M. N. Plana, K. H. Nicolaides

First published: 27 July 2017 Full publication history

DOI: 10.1002/uog.17484 View/save citation

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Detection Rate and False Positives

- T21: 30 different studies reporting more than 200,000 patients with known outcome. DR is 99.7% and FPR is 0.04%.
- T18: DR is 98% and FPR is 0.04%.
- T13: DR is 99% and FPR is 0.04%.
- Failed test due to low fetal DNA fraction varied widely from study to study. Overall, seems to be about 1% of samples.

Advantages of cff-DNA Testing

- High sensitivity for common trisomies.
- Super low false positive rate.
- No need for NT ultrasound.
- Can be run from any office.
- Even homebirth midwifes are using this technology.

Need for confirmatory testing

- Imagine a 28 year old patient with a positive NIPT for T21. What is the probability that her pregnancy is really affected?
- Consider that prior probability of T21 is about 1:1000.
- FPR for the test is on the order of about 0.04% or about 1/2000.
- This means that the chance of a true positive is about 2/3 and chance for false positive is about 1/3.
- Clearly, the patient needs to consider confirmatory testing.

Limitations:
What will cff-Fetal DNA (NIPT) miss?

- Multiple studies with similar conclusions:
- Reliance on NIPT will miss things - common trisomies are simply NOT the whole story of fetal chromosome abnormalities.
- This is especially true if you include micro-chromosome abnormalities.
- Remember: Micro-chromosome abnormalities (collectively) affect 1% of all pregnancies

Limitations

- Will not detect unusual chromosome abnormalities.
- Will not detect micro-chromosome abnormalities.
- As companies try to fill these gaps, they increase false positives.
- In talking with patients, I emphasize the trade off:
  cff-Fetal DNA testing has no risk and yields less information.
  Amnio/CVS yields more information but has some risk.

Study to assess what NIPT misses

- Retrospective analysis of California state maternal serum screening program data.
- 1,324,607 women screened (FTS, Quad, Sequential and Integrated)
- 68,990 (5.2%) screened positive.
- Of these, 26,056 (38%) had amnio/CVS.
- Of these 2993 (11%) had abnormal result.
- Goal of study was to ask what % would be detected by NIPT.

Results:

- Predictions about sensitivity of NIPT for various disorders seems reasonable. Considered sex chromosome anomalies to be detectable.
- Overall, 16.9% of abnormal results were considered undetectable by NIPT.
- Most likely, there is some bias. Women who chose amnio/CVS probably were more likely to have ultrasound anomalies, increasing the chances of atypical chromosome abnormality.
- However, this study did not address micro-chromosome abnormality, so the true % is probably higher.

Table 4. Distribution of Chromosomal Abnormalities Identified by Current Prenatal Screening and Predicted Detection by Noninvasive Prenatal Testing: Patterns by Age Groupings

	Maternal Age at Term (y)		
	Younger Than 25	25–29	30–34
Any chromosomal abnormality	220	360	638
Detectable by noninvasive prenatal testing	178 (80.9), (75.7–86.1)	275 (76.4), (72.0–80.8)	529 (82.9), (80.0–85.8)
T21	96 (43.6)	148 (41.1)	346 (54.2)
T18	27 (12.3)	61 (16.9)	83 (13.0)
T13	12 (5.5)	13 (3.6)	30 (4.7)
Sex chromosomal aneuploidy	43 (19.6)	53 (14.7)	70 (11.0)
Not detectable	42 (19.1), (13.9–24.3)	85 (23.6), (19.2–28.0)	109 (17.1), (14.2–20.0)
T21—mosaic	—	—	3 (0.5)
T18—mosaic	1 (0.5)	—	2 (0.3)
T13—mosaic	—	1 (0.3)	—
Sex chromosomal aneuploidy—mosaic	5 (2.3)	10 (2.8)	8 (1.3)
Other trisomies			
Not mosaic	9 (4.1)	18 (5.0)	21 (3.3)
Mosaic	4 (1.8)	4 (1.1)	9 (1.4)
Balanced rearrangements			
Not mosaic	7 (3.2)	14 (3.9)	24 (3.8)
Mosaic	—	1 (0.3)	—
Unbalanced rearrangements			
Not mosaic	—	—	—
Insertions and deletions			
Not mosaic	11 (5.0)	26 (7.2)	24 (3.8)
Mosaic	—	1 (0.3)	1 (0.2)
Triploidy			
Not mosaic	3 (1.4)	4 (1.1)	10 (1.6)
Mosaic	—	—	1 (0.2)
Tetraploidy			
Mosaic	—	—	—
Extrastructurally abnormal chromosome			
Not mosaic	1 (0.5)	—	2 (0.3)
Mosaic	—	1 (0.3)	—
Confined placental mosaicism	1 (0.5)	5 (1.4)	4 (0.6)

Data are n; n (%), (95% confidence interval); or n (%) unless otherwise specified.
* Not computed, frequency of one or more cells less than 5.

Overall Conclusion

- In women who screen positive with conventional testing, whether its 5% or 20%, there is no doubt that NIPT will not detect a substantial proportion of chromosome abnormalities.
- The proportion is expected to be greater in the setting of abnormal ultrasound findings.
- No study addresses what % of abnormalities will be missed in a low risk population, but one can estimate 2-3%.
- Patients understand that NIPT cannot detect everything, but generally perceive their risk as low and the risk of invasive testing as being too high.

Twins and NIPT

- Conventional screening with NT and serum markers works poorly in twin pregnancies. Sensitivity for T21 is about 70% and screen positive rate is at least 10%.
- In principle, cff-DNA should work just about as well in twin pregnancies as in singletons.
- If monozygotic, then there is no reason to suspect that performance will be worse than in singletons.

Dizygotic Twin Pregnancy

- If dizygotic, then the most likely abnormal scenario would be that one twin is affected and the other is normal.
- Imagine that cff-DNA is 90% maternal and 10% fetal, with 5% coming from one twin and 5% coming from the other. The normal twin simply contributes to the normal maternal background.
- This situation is basically the same as singleton pregnancy with 5% fetal DNA.
- If a fetal fraction of 4% is needed for singleton test, then 8% should be sufficient for twins.

Prospective Data?

- No huge studies available.
- A series of small studies all show the same thing: 100% sensitivity for DS and T18 (except one study that had a single false negative).
- Overall performance is similar to singletons except for higher % of cases with insufficient fetal DNA.

Recommendations?

- I tell “high risk” women that, if they want aneuploidy screening, this is the way to go.
- However, most insurers will not cover NIPT in the setting of twins.
- Out of pocket expense is likely to be worth it for many patients.
- I try to get them to do it early in pregnancy, so that CVS will still be possible.
- If you end up with a diagnosis of trisomy, earlier is better.

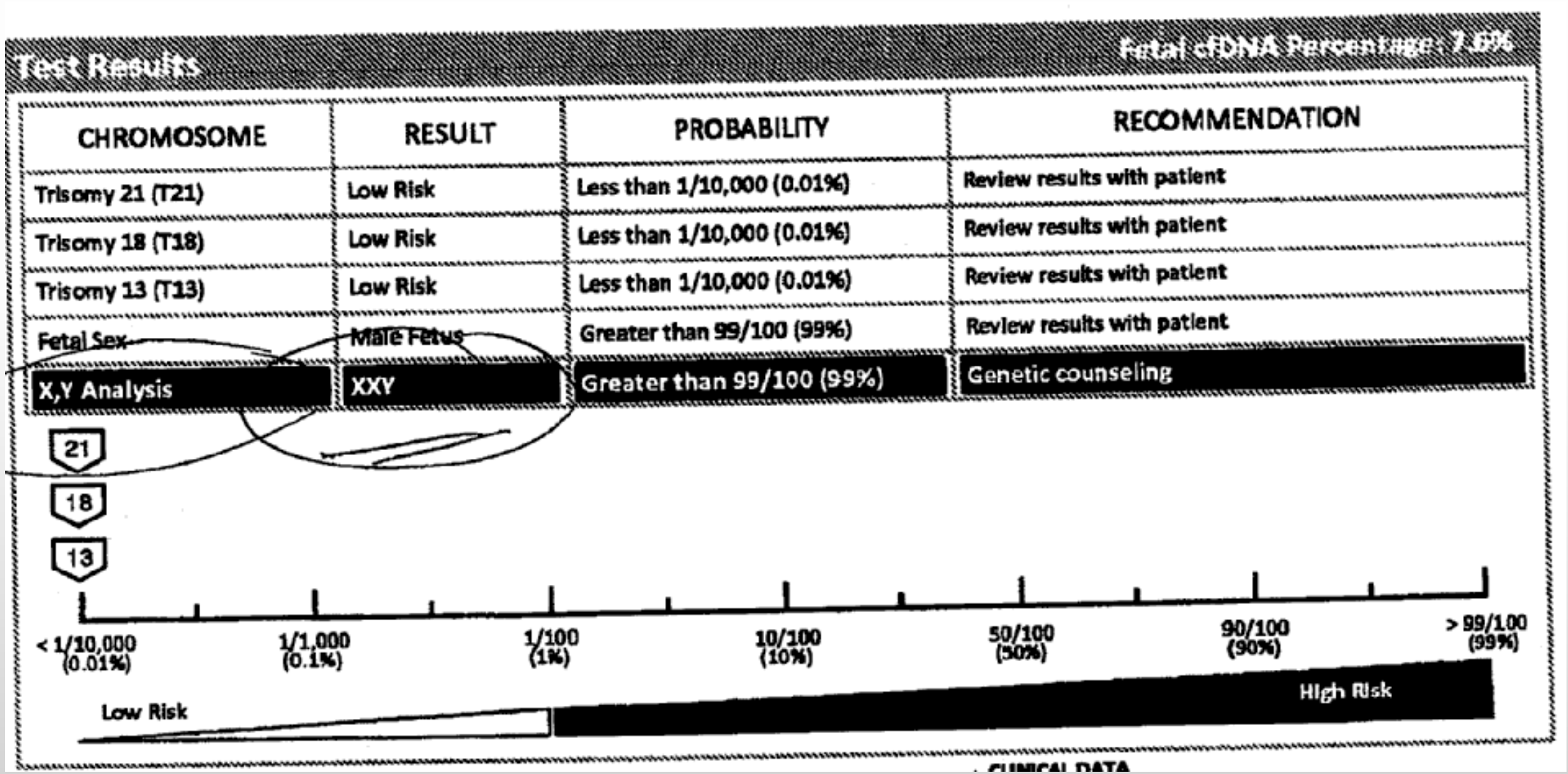
Expanding NIPT

- Initially intended for detection of common trisomies, 13, 18 and 21.
- Each company wants to claim their test is better than the competitors.
- Now, all companies claim good ability to detect sex chromosome abnormalities: 45,X; XXY, XYY and XXX.
- Some companies claim ability to detect specific micro-chromosome abnormalities, such as 22q deletion and others.

Sex Chromosome Abnormalities

- There is a huge ethical and moral question about whether or not to screen for sex chromosome abnormalities.
- There are NO professional society guidelines endorsing such screening.
- General public has VERY little understanding of sex chromosome abnormalities.
- If screening is to be done, patients should be educated and informed – which is totally impractical.

NIPT for Sex Chromosome Abnormalities



NIPT for Sex Chromosome Abnormalities

- Labs make it sound like tests are basically diagnostic.
- Do not be fooled: PPVs are not that high.
- Studies that have assessed PPV for XO, XXY, XYY and XXX have shown that they are generally less than 50%.
- Several reasons for this:
  First, prevalence is not very high - 1:500 to 1:1000.
  Second, maternal mosaicism for X chromosome aneuploidy and Y chromosome polymorphic variants make detection of true aneuploidy technically challenging.

What to do?

- No right answer.
- Doctors and midwifes in our group disagree on routine testing for sex chromosome abnormalities.
- In my case, I go on a case by case basis. If a patient/couple seems like they would want to pursue SCA, I explain the possibility to them. In general, I do not.

Micro-chromosome Abnormalities

- Affect at least 1% of pregnancies.
- Overall, are a bigger cause of developmental disability than DS.
- Not age related
- Most do not have major malformations that would be detected by ultrasound.
- Most occur at random and are either unique or nearly unique.
- A few are recurrent - e.g. 22q, 15q, 5p etc..
- It would be nice to have non-invasive screening.

NIPT for Micro-abnormalities

- In principle, works just like detecting trisomy.
- Research studies have shown that it is possible to use NIPT to detect some micro-abnormalities.
- Clearly very technically challenging and limited to larger abnormalities – even in research studies.
- Companies have come out with claims that their test can detect specific recurrent microdeletions.

Syndrome	MaterniT21 PLUS ESS	Verifi PLUS	Panorama	NIFTY
22q11.2 (DGS)	√	√	√	X
5p (cri-du-chat)	√	√	√	√
15q (PWS/AS)	√	√	√	√
1p36del	√	√	√	√
Wolf-Hirschhorn	√	√	X	X
Langer-Giedion	√	X	X	X
Jacobsen	√	X	X	√
Van der Woude	X	X	X	√
DGS2	X	X	X	√
16p12	X	X	X	√
2q33.1	X	X	X	√

Problems with NIPT for micro-deletions

- In general, sensitivity, specificity and PPV are not well known.
- Except for 22q, none occur with enough frequency to make it possible to do a prospective validation study.
- Existing validation studies are not prospective don’t really address PPV.
- In the one major effort to validate routine screening for 22q, sensitivity was not determined and PPV was lousy.
- Performance would be worse for less common abnormalities.

NIPT for Micro-abnormalities

- In my opinion, routine screening for micro-abnormalities will never achieve a very good sensitivity and will add a lot to false positive rates.
- Patients may be falsely reassured.
- I tell patients that, if they really want to exclude micro-abnormalities, they need amnio or CVS.
- This is particularly true in the setting of ultrasound abnormality.

Summary

- NIPT works really really well as a screening test for common trisomies.
- Works well in twin pregnancies, but insurance generally will not cover.
- Reliance on NIPT in the setting of abnormal conventional screening has a reasonable probability to miss atypical chromosome abnormalities.
- NIPT is not and probably never will be very useful for detection of unusual chromosome abnormalities and micro-abnormalities.
- What to do about routine screening for sex chromosome abnormalities is an open and difficult question.

Questions?

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OB/GYN Webinar Series 2017-2018
Special Series: Genetic Testing with Dr. Stephen Brown

Thursday, February 8th, 12pm- 1pm EST
Expanded Carrier Screening

Thursday, February 15th, 12-1pm EST
Conventional Aneuploidy Screening: Does it still have a place?

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