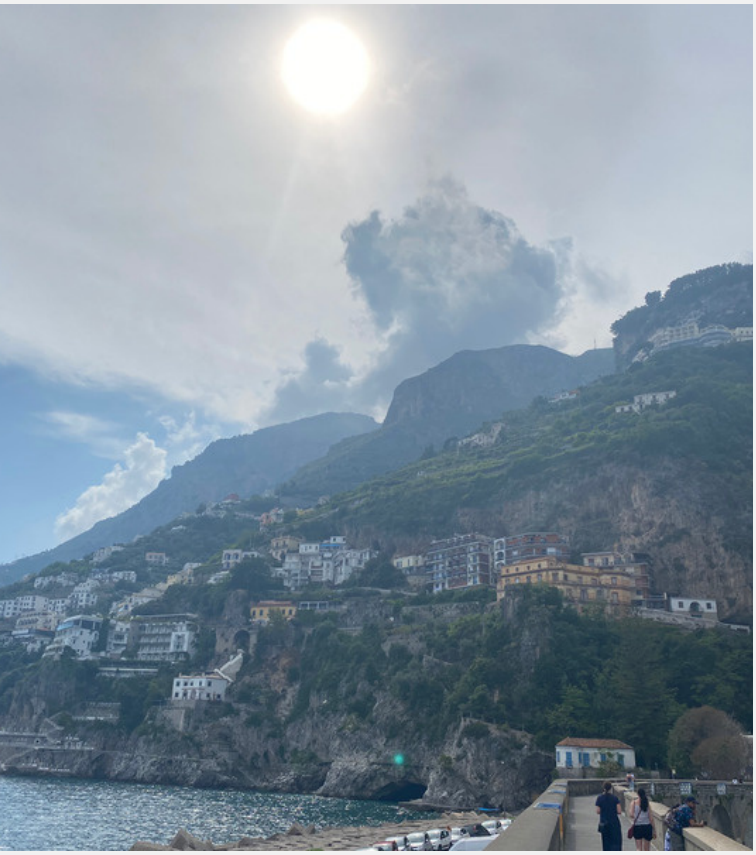
NEWSLETTER



INTRODUCTION

This newsletter centers on reproductive topics with a genetics focus. If there is an organization or upcoming webinar you'd like me to include in a future newsletter, please feel free to reach out at genetics@modernreproduction.org.

Sign up for the newsletter here

What to expect

when you're expecting this newsletter

The little lit review

Patient facing content

Provider resources

Modern Reproduction Content

NEWSLETTER

The little lit review

1

Position statement from the International Society for Prenatal Diagnosis on the use of noninvasive prenatal testing for the detection of fetal chromosomal conditions in singleton pregnancies

Lisa Hui, Katie Ellis, Dora Mayen, Mark D. Pertile, Rebecca Reimers, Luming Sun, Joris Vermeesch, Neeta L. Vora, Lyn S. Chitty on behalf of the ISPD Board of Directors

This new position replaces the 2015 position statement.

Reminders:

- Confined placental mosaicism (CPM) occurs in 1%–2% of pregnancies and can be a cause of false positive NIPT results.
- Some chromosome abnormalities such as trisomy 13 and monosomy X have higher risks of CPM and amniocentesis may be preferred over chorionic villus sampling (CVS), if no fetal ultrasound abnormalities are present and patient is open to waiting
- Fetal fraction varies between individuals and by other factors such as gestational age, maternal weight, maternal race, fetal karyotype, and maternal medical conditions
- Cost and health policies influence whether cfDNA can be a primary or contingent offer
- Validation utilizing clinical studies are challenging because of the rarity of some conditions detected with expanded NIPT as well as the phenotype variability
- 97% of all rare autosomal trisomies (RATs) detected in CVS appear to be confined to the placenta and not present in the fetus
- While this may vary depending on the implicated chromosome, there is about a 2.1% risk for UPD in the event of perceived trisomy rescue
- Many pathogenic CNVs are below the limits of resolution of genome-wide NIPT
- 16.1% of pregnant patients have an ultrasound finding at the time of NIPT blood draw that would have altered the provider's counseling, such as a fetal structural anomaly, incorrect dating, multiple gestation, or nonviable pregnancy
- A NT ≥3.5mm is associated with a variety of conditions that are not detectable on NIPT, including atypical chromosome abnormalities, single gene conditions, and structural malformations
- Posttest counseling for those with low chance results should include a caveat that NIPT does not exclude all genetic conditions and that false negative results may occur.

Recommendations:

- cfDNA screening has high accuracy compared to other screens, yet diagnostic testing is still recommended, especially prior to termination of pregnancy, if selected.
- Labs should determine fetal fraction (FF) thresholds with internal validation and protocols for suspected maternal malignancy
- Clinicians should develop "no call" protocols - Options include: detailed ultrasound, offer of repeat NIPT, alternative screening test, and/or diagnostic testing.

NEWSLETTER

The little lit review

Recommendations Con't:

- Accuracy of sex chromosomal aneuploidy (SCA) is sufficient to order alongside the common aneuploidies, though downstream effects should be studied, particularly in the cultural/social/ethical context
- There is insufficient data to assess the performance and clinical utility of routine NIPT for RATs.
  - If performed and due to the high likelihood of CPM underlying a positive NIPT result for a RAT, amniocentesisis the single most informative test for fetal karyotype. UPD studies should be included if imprinted chromosome is implicated (6, 7, 11, 14, 15, 20)
- NIPT for subchromosomal imbalances ormicrodeletion/microduplication syndomes is not recommended for the routine care of unselected populations
- At least one early first trimester scan for dating, diagnosis of multiple pregnancy and confirmation of fetal viability should be offered before performing NIPT
- Fetus with ultrasound abnormalities, including NT measurement ≥3.5 mm, should be offered diagnostic testing and evaluation with chromosomal microarray regardless of the prior NIPT result. There is no consensus on the use of alternative NT thresholds (such as 3.0 mm or 99th centile) for defining a population that should be offered diagnostic testing.
- Principles of informed choice should be maintained in the face of routinization of prenatal screening and the expanded scope of some NIPT assays

Implementation of Exome Sequencing in Prenatal Diagnostics: Chances and Challenges

A few years ago, I listened to a MFM and senior GC discuss their experience with WES in prenatal cases. At the time, I'd ordered a few research WES and one clinical WES, so I expected them to say that WES will be the new normal. However, from their experience, they found that many of the diagnoses made would have been detected via targeted gene panels and a discerning genetics eye. Ordering WES was cheating and not the first line test.

While WES is still not considered a first line test even after these few years and microarray still reigning, it is still advantageous to explore studies in which WES is performed. This article saliently remarks one of the largest challenges with prenatal WES is "correlating the genotype with the prenatal phenotype. In general, the fetal phenotype of many conditions has not been well described and may deviate quite substantially from the known postnatal phenotype." However, this challenge underscores the benefit of WES as there are wide phenotype variability for many genetic syndromes. This article reviews the experience of a single center in which 7 of the 28 cases were provided a diagnosis and the TAT was under 4 weeks.

NEWSLETTER

Patient Facing Content

Youtube

Youtube university is the best. You can learn how to change your water heater as well as considerations for trying to conceive from Board Certified Reproductive Endocrinologist, Dr. Morris. Other popular physicians on Youtube include: Dr. Crawford, The Doctors Bjorkman, Midwife Kira and Dr. Goodall McDonald.

DR SERENA CHEN ON WIRED

Genomics Education Programme offers clinician focused content on genomics.

My PGT-M Case was Declined

A difficult conversation to have with a patient is when a their case is declined by a PGT laboratory, particularly if the patient had their reproductive plans set on utilizing PGT-M for their family building. This blog post dives into the reasons why a case may be declined.

Of note-

Unfortunately, Juno Diagnostics will no longer offer their noninvasive prenatal screening.