Limitations of noninvasive aneuploidy screening in general. Limitations of non invasive maternal serum Fetal DNA (NIPT) after high risk FTS nuchal translucency / nasal bone and biochemical analyte screening

Aneuploidy screening or diagnostic testing should be discussed and offered to all pregnant women.
*Practice Bulletin -Screening for Fetal Aneuploidy. ACOG. Society Maternal-Fetal Medicine. May 2016.

In the AMA population there is a 1.7% incidence of clinically significant pathogenic copy number variants PCNV - genetic abnormalities that will only be detected by microarray technology from CVS or amniocentesis specimens even after normal standard metaphase cytogenetics results. These abnormalities will not be detected by fetal DNA.

For patients of any age even with normal ultrasound, low risk results from FTS NT / NB and fetal DNA and even with normal cytogenetic karyotype, the chance of a pathogenic copy number variant is greater than 1%, similar to the age related risk of aneuploidy in the fetus of a 38 year old. This risk is 4 fold higher than the risk of trisomy 21 in a woman younger than 30 and 5- to 10- fold higher than the presently accepted risk of CVS or amniocentesis (1:<400; <0.25%.)

About 1% of all children develop neurologic developmental delays, and over 1% develop autism. Chromosomal microarray studies suggest that as much as 50% of neurologic developmental delays and 20% of autism can be identified.

Consideration should be given to patient education - regardless of age - of these risks and be offered the opportunity to have a diagnostic CVS or amniocentesis to include microarray and if fetal malformations are identified - trio whole genome sequencing.
*Wapner. N Engl J Med 2012; 367:2175-2184.
*Evans. Noninvasive prenatal screening or advanced diagnostic testing: caveat emptor. AJOG. Sept 2016.
*Evans. Prenatal Diagnosis. 2018;38:243-245.
*Rosenfeld. J Pediatr Gen. 2017;6:42-50.

Limitations of non invasive maternal serum Fetal DNA (NIPT) after high risk FTS nuchal translucency / nasal bone and biochemical analyte screening

Most submicroscopic atypical aberrations are pathogenic copy-number variants (pCNVs), a heterogeneous group of structural chromosomal aberrations that are individually rare but, in women younger than 36 years of age, collectively more frequent than trisomy 21. pCNVs vary in phenotype but may have severe sequelae, which is why early prenatal diagnosis is warranted.

Replacing invasive testing with non invasive maternal serum Fetal DNA (NIPT) for patients screened high-risk by first trimester nuchal translucency / nasal bone and biochemical analytes (combined FTS) would substantially decrease the first-trimester detection of pathogenic chromosomal anomalies. Following a high-risk combined FTS result, 1 in every 26 pregnancies would be affected by a fetal chromosomal aberration, despite a normal NIPT result.

Most of the pCNVs are small - 79% were shorter than 5 Mb and would not be detected by genome-wide NIPT. Using genome-wide NIPT platforms capable of detecting aberrations > 5 Mb would only reduce the residual risk to approximately 1 in 34 pregnancies.

*Gadsbøll. Combined first-trimester screening and invasive diagnostics for atypical chromosomal aberrations: Danish nationwide study of prenatal profiles and detection compared with NIPT. Ultrasound Obstet Gynecol, 64: 470-479. https://doi.org/10.1002/uog.27667