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Look Before You Leap: The Clinical Value of Genome-Wide NIPT

Announcer: You're listening to ReachMD. This medical industry feature, titled "Look Before You Leap: The Clinical Value of Genome-Wide NIPT" is sponsored by Roche Diagnostics. Here's your host, Dr. Jennifer Caudle.

Dr. Caudle: Understanding how genome-wide NIPT works and impacts prenatal care is critical for determining if this type of NIPT makes sense for your practice and whether the potential benefits outweigh the drawbacks, which is exactly why this technique will be the focus of today's discussion.

This is ReachMD, and I'm your host, Dr. Jennifer Caudle. Joining me to discuss the expanding NIPT menu options is Dr. Liza Kunz, Board Certified Maternal-Fetal Medicine Physician and Medical Director at Roche Sequencing Solutions. Thanks for being here today, Dr. Kunz.

Dr. Kunz: Thanks so much for having me.

Dr. Caudle: Absolutely. So, why don't we just start right at the beginning. What can you tell us about whole-genome screening, or WGS?

Dr. Kunz: It's important to recognize that whole-genome sequencing is not the same thing as "genome-wide NIPT." Whole-genome sequencing is a diagnostic technique that really helps us find answers for families where traditional karyotype or microarray didn't find a genetic change to explain what was seen in the phenotype. It's much more used in the pediatric space than antenatally because it provides a base-by-base review of the genome to capture large and small variants that would otherwise be missed. There are some ongoing studies looking at utilizing this technology when ultrasound demonstrates abnormalities and the amniocentesis results after a microarray are not informative.

"Whole-genome or genome-wide NIPT," on the other hand, is actually something very different. There are 2 main categories of NIPT that are currently on the market, targeted approaches and MPSS approaches.1 In targeted approaches, only the chromosomes of interest for screening are analyzed, typically chromosomes 21, 18, 13, X and Y. Massive parallel shotgun sequencing (MPSS) spends a lot of sequencing capital on the other chromosomes that really weren't of interest because it can't differentiate on the front end the chromosome needed for reporting a result. Then they used bioinformatics tools to mask the unwanted data after the sequencing. Whole-genome sequencing is just the unmasking of that data and then trying to build a medical value story around it. 2

Dr. Caudle: So, how does Genome Wide NIPT differ from the microdeletion panels that we've seen on NIPT menus?

Dr. Kunz: Genome wide NIPT is the screening for RATs, or rare autosomal trisomies. RATs are an extra copy of a chromosome other than 13, 18, 21, X or Y, so when RATs are identified in the fetus in a non-mosaic state, they're not compatible with ongoing pregnancy and would cause a miscarriage. In a mosaic state, however, the impact is not necessarily clear or consistent, especially since you could have RATs in a mosaic state that are confined to the placenta.3-8

Copy number variants, or CNVs, are segments of DNA that are extra or missing, and this may or may not correlate with a known genetic syndrome. In the case of whole-genome NIPT, only CNVs greater than 7 megabases in size can be reliably identified.9-10

Dr. Caudle: So, now that we know the difference between them, Dr. Kunz, why would I want to screen my patient for RATs or CNVs?

Dr. Kunz: There are 2 contexts where whole-genome screening is typically considered. The first is an asymptomatic patient who expresses a desire to test for everything. The second is a patient where an anomaly is seen on ultrasound but she's hoping to avoid an invasive procedure. I hope I can explain why whole-genome screening is not appropriate for either scenario.

We know that there are many CNVs, hundreds of them in fact, that can be associated with poor pregnancy outcome. Unfortunately, many of these CNVs, in fact 70% of them, are smaller than 7 megabases in size and will not get picked up by the screening. If a disease causing CNV is detected, this information could better inform expectant parents and enhance their ability to plan for the child's future.9

Identifying a RAT in a non-viable pregnancy may give an answer to a family that wants to know why a miscarriage occurred. It's also important to note that there is some association between rare autosomal trisomies and poor pregnancy outcomes, such as growth restriction or preeclampsia.10

Dr. Caudle: And once a RAT or CNV has been identified in a pregnant patient, how does that affect how I manage that patient then?

Dr. Kunz: If a CNV is detected by NIPT, confirmatory testing is essential. Given the very rare incidence of these in the population, the positive predictive value is actually quite low, typically less than 5% and sometimes less than 1%. If the CNV is confirmed by diagnostic testing, a clinician could combine this result with ultrasound findings to counsel the family about expected outcomes. In the well over 90% of cases where this is a false positive, the effect would be an unnecessary invasive procedure. In addition, CNVs can be unique and previously unidentified with very uncertain phenotypes. They can range from normal to significant disabilities, many of which are not visible on ultrasound, so the counseling in these cases of a detected CNV is quite complex.10

If a RATs identified, however, the management is even more complex. Confirmatory testing is again essential, but it is not clear that simply an amniocentesis OR a CVS gives the complete picture. BOTH invasive tests would be necessary to evaluate for confined placental mosaicism (CPM), the condition which is potentially associated with adverse pregnancy outcomes. And unfortunately, we don't yet have enough data to know how often confined placental mosaicism may be present in routine populations, or if a certain level of mosaicism would be more likely pathogenic. A pregnancy that's "complicated" by CPM may have a normal outcome, or it may be complicated by severe growth restriction or severe early onset preeclampsia. And since there's no treatment modality that modifies these outcomes, I would just need to watch and wait with blood pressure monitoring and serial ultrasounds.10

Dr. Caudle: You know and I guess just to look at this from the other side, Dr. Kunz, what about a screen-negative RAT and CNV result? How would that clarify prenatal care, especially for patients who have an ultrasound anomaly?

Dr. Kunz: Patients often want to avoid a diagnostic test. As I mentioned, there are many pathogenic CNVs that are smaller than the 7 megabase size that can't be detected by the screening, so any patient with an ultrasound anomaly really needs a diagnostic test to be appropriately counseled. If I get a positive screen, I need a confirmatory test. If I get a negative screen and I'm still seeking a diagnosis, I need the diagnostic test. Adding screening to the care of a patient with an ultrasound anomaly only lengthens the diagnostic journey and adds expense. 10

Dr. Caudle: And before we wrap up, Dr. Kunz, what else should we know about whole-genome NIPT, and are there other limitations we should also be aware of?

Dr. Kunz: I think it's essential to realize that the lack of evidence demonstrating the clinical value of screening for RATs and CNVs has compelled professional societies to advise against its use. 11-12

Essentially, there's no evidence, no clinical studies, demonstrating that investigating RATs may improve clinical management of pregnancies. Microdeletions and duplications are potentially covered by this method, but we don't yet know what the sensitivity is for these conditions, so essentially, when a woman tests negative and she has a high a priori risk, the posterior risk is still extremely high. If the test result is positive, then a woman should undergo a confirmatory procedure because of the low PPV of the conditions under investigation. The test result does not affect the management of the pregnancy. 10

Lastly, introducing a screening test with unknown performance and unproven clinical value can lead to uncertainty regarding the reliability of the result, increase complexity of patient care and counseling, unnecessary invasive procedures and undo patient anxiety.12 It's possible that the availability of genome wide NIPT has been driven more by the technical feasibility than true clinical value.

Dr. Caudle: That's very interesting, and I think one of the biggest takeaways here is that there is a lot to consider, and we should approach these new tests with caution.

I'd really like to thank you, Dr. Kunz, for helping us better understand all of that. It was really great speaking with you today.

Dr. Kunz: It was wonderful to be here.

Announcer:
This program was sponsored by Roche Diagnostics. If you missed any part of this discussion visit ReachMD.com/genome-wide-NIPT. This is ReachMD. Be part of the knowledge.

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