Reducing the Anxiety of Prenatal Testing
A genetic counselor discusses cell-free DNA NIPT and the value of high accuracy, low failure rate options such as the verifi® Prenatal test.

Introduction
With an undergraduate degree in molecular biology, Jake Massa entered his first job with every intention of attending medical school after a few years. Much to his surprise, he discovered a career that was a better fit. “Part of my responsibilities in the clinical DNA diagnostics laboratory at Children’s Mercy Hospital was to talk with genetic counselors about DNA test results. I had never heard of the career before and began asking questions about what they did.” The more questions he asked, the more he realized that genetic counseling was the profession for him.

Jake changed career paths and earned a Master of Science in Medical and Molecular Genetics, Genetic Counseling at Indiana University in 2007. Next, he embarked on a more than 8-year career as a Genetic Counselor at Kaiser Permanente Medical Centers in northern California.

Counseling prenatal patients accounted for about 40% of Jake’s job responsibilities while at Kaiser. He educated patients and reviewed the results of a wide range of prenatal tests, including maternal serum screening, various types of ultrasounds, noninvasive prenatal testing (NIPT), and diagnostic tests such as chorionic villus sampling (CVS) and amniocentesis. His NIPT counseling experience included discussing the reasons why NIPT test failures occurred, and the next steps required to confirm or rule out aneuploidy.

Jake joined Illumina in August 2015 as a genetic counselor working within the Reproductive and Genetic Health business unit providing clinical support for the verifi® Prenatal test. iCommunity spoke with him about his experience as a hospital-based genetic counselor, and the value of low failure, fast turnaround next-generation sequencing (NGS)-based cell-free DNA (cfDNA) NIPT such as the verifi Prenatal test.

Q: What prompted you to become a genetic counselor?
Jake Massa (JM): During my conversations with genetic counselors at Children’s Mercy Hospital, I asked them about the qualities that were needed to be successful at the job. I kept hearing the same 4 traits. A love of math and science, particularly genetics probability statistics. A thirst to learn, because the field of medical genetics and genomics was, and still is, changing at an incredible pace. A genuineness when working with people who are under stress, who are grieving over the loss of a child or perhaps are very ill themselves. Finally, an ability to understand and share the perspective of the patient. Those 4 qualities drew me in and prompted me to apply for graduate programs.”

Q: What was the range of experience that you gained during your more than 8 years at Kaiser?
JM: Most genetic counselors specialize in a specific discipline such as prenatal genetics, pediatric genetics, or hereditary cancer susceptibility. However, at Kaiser, genetic counselors have the option to see a wide variety of patients. Prenatal counseling made up 30–40% of my patients.

Initially, I spent my time reviewing the results of maternal serum screening, 20-week fetal anatomy and first trimester nuchal translucency ultrasounds, and invasive diagnostic tests such as CVS and amniocentesis. In 2012, NIPT became available and I began discussing the results of the Ariosa Harmony NGS-based cfDNA NIPT with certain patients.

Q: How did you incorporate cfDNA NIPT into your prenatal test offering at Kaiser?
JM: The physicians and genetic counselors met, we looked at the evidence, and decided to offer cfDNA NIPT. In the beginning, we reevaluated the decision every so often based on the numbers we were seeing. Over time, there was a building body of evidence that supported use of cfDNA NIPT for a growing list of indications. We were also becoming comfortable with cfDNA NIPT as we built our clinical experience around it.

Q: When did you use cfDNA NIPT and maternal serum screening tests?
JM: Kaiser made decisions from the standpoint of being the payer and the medical care provider. In 2012, we set criteria for offering the test based on the evidence. We offered NIPT for high-risk patients, including those of advanced maternal age, who had a positive maternal serum screening test or an ultrasound finding that was consistent with an increased risk for an aneuploidy, or who had a previous child or pregnancy that had an aneuploidy covered by cfDNA NIPT.

Jake Massa is currently a genetic counselor at Illumina. Previously, he was a genetic counselor at Kaiser Permanente Medical Centers for 8 years.
In contrast, we didn’t offer cfDNA NIPT to patients who were at low risk for aneuploidy. That was still the case when I left Kaiser in 2015.

The turnaround time of serum screening and the Harmony cfDNA NIPT was the same at 7–10 days. If patients had a high-risk result from one or the other, or both, they were offered the option of having an invasive diagnostic test.

“Laboratories with high technical failure rates might be missing more aneuploidies.”

Q: What are some of the causes of cfDNA NIPT test failures?
JM: There are 2 types of cfDNA NIPT test failures. Administrative test failures occur when there is a problem with the sample before it arrives at the testing laboratory. Common issues include improper labeling of the sample, improper phlebotomy technique, poor shipping conditions, too small of a sample, or the blood draw was taken too early in the gestational age. The second type of test failure is a technical failure. These are the failures that occur during the testing process and after the sample is received by the lab.

Q: How do cfDNA NIPT failure rates differ?
JM: Unfortunately, there isn’t a lot of failure rate information on array-based cfDNA NIPT products, such as the Ariosa Harmony test, since they are relatively new to the market. For targeted sequencing, cfDNA NIPT, such as the Natera Panorama test, the failure rate is 3.8%.1 For whole-genome sequencing cfDNA NIPT, the Sequenom MaterniT21 technical failure rate is 1.3%,2 while the Illumina verifi Prenatal test has a technical failure rate of 0.1%3.

Q: When is there a test failure, how does that affect the test metrics?
JM: cfDNA NIPT technical failures can affect several test metrics. We know there is a high rate of aneuploidy in technical failures, with the rate of aneuploidy as high as 1 in 5 failed samples.4 That means these technical failures are, in fact, high-risk results for the patient. Laboratories with high technical failure rates might be missing more aneuploidies. If these technical failures are counted in the negative column of their test performance calculations, their test sensitivities will be significantly lower. Alternatively, if those same labs include these technical failures as high-risk results in their test metrics, then their test specificity and positive predictive value (PPV) will be lower.

Labs with high failure rates force clinicians to treat a large number of failures as high-risk results. This causes patients to consider having invasive diagnostic procedures, such as CVS or amniocentesis, when their pregnancy is in fact normal. Thus, high technical test failure rates could lead to an uptake in diagnostic testing and procedural-related pregnancy losses.

Q: What is PPV?
JM: PPV is the likelihood that an abnormal screening test is actually correct. In the case of cfDNA NIPT, it is the chance that the fetus is affected with aneuploidy when a cfDNA NIPT test result is positive. In general, high sensitivity and high specificity leads to higher PPV for any screening test. However, high prevalence of a given aneuploidy condition also leads to higher PPV in cfDNA NIPT. That’s why maternal age can be a factor. The higher the maternal age, the increased chance of aneuploidy. Therefore, the PPV of cfDNA NIPT increases as a woman’s a priori aneuploidy risk increases.

For example, a younger woman’s a priori aneuploidy risk is low. If her cfDNA NIPT results are abnormal, the PPV of the cfDNA NIPT test is lower. If the woman is older, her a priori risk is higher for aneuploidy and an abnormal NIPT test will have a higher PPV when compared to the younger woman.

Q: Did you discuss failure rates and PPV with patients before they underwent cfDNA NIPT?
JM: I would discuss the concepts of screening versus diagnostic testing, and the possible results of each type of test in a pre-test counseling scenario. I discussed test failure rates in those meetings, which often led into a discussion about the ideas behind PPV. However, I wouldn’t use the term PPV because it is a foreign concept to most people and can be off-putting.

Q: What were your patients’ reactions to cfDNA NIPT failure rates?
JM: Patients’ reactions to hearing about failure rates, especially if they experienced a failure, ranged from annoyance or frustration to disappointment and anxiety. I found that when I explained the possibility of a failure up front and prepared them for a worst case scenario, they would react to the situation constructively. However, I definitely experienced patients’ negative reactions when test failures occurred.

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Q: How did you counsel patients when there was a test failure?
What were the next steps?
JM: We typically offered a redraw for the initial failure unless the patient’s window for diagnostic testing was closing. If a second failure occurred, we then discussed the options of maternal serum screening and diagnostic testing depending upon the patient’s gestational age.

Q: Why did you choose to join Illumina?
JM: The job at Illumina was really a great opportunity to work with a company that leads the industry in several different ways and learn more about NIPT technology. Although I hadn’t used the verifi Prenatal test before, I was very aware of its low failure rate. I’d seen how frustrating it was for my patients who had to deal with test failures. I wanted to work with a company that offered a high-quality NIPT test.
Q: How does the verifi Prenatal test compare to the Harmony test you used at Kaiser? JM: The verifi Prenatal test has a lower failure rate and shorter turnaround time than the Harmony test I offered while at Kaiser, which was the original NGS-based Harmony test (it’s now on a microarray-based platform). The verifi technical failure rate of 0.1% is substantially lower than that version of the Harmony test, which was 3.0% after a redraw. The failure rate for the new, microarray-based Harmony test is unknown. The typical turnaround time for Harmony is 7–10 business days, in contrast to 3–5 business days for the verifi Prenatal test.

“The verifi Prenatal test has a quick turnaround time and a low failure rate.”

Q: How are laboratory professionals and genetic counselors benefitting from the cfDNA NIPT options such as the verifi Prenatal test? JM: cfDNA NIPT screening is a much more accurate screening test for certain aneuploidies when compared to maternal serum screening. Evidence continues to build for its use in the obstetric population, including with low-risk groups. More accurate cfDNA NIPT screening for patients means that fewer invasive diagnostic procedures will need to be offered and performed. This means fewer patients are faced with stressful decisions regarding diagnostic testing. cfDNA NIPT also offers a better patient experience. The verifi Prenatal test has a quick turnaround time and a low failure rate. The result is that patients are reassured about their pregnancies sooner, and are less likely to deal with the confusing and anxiety inducing situation of a technical failure. If the patient is happier with her experience, then Illumina clinical laboratory partners are going to benefit as well.

Q: Since mid-2015, has there been increased awareness of the value of cfDNA NIPT, such as the verifi Prenatal test? JM: The verifi Prenatal test was one of the early NIPTs on the market, so it was well known before I ever came to Illumina. Because of statements released recently by the American College of Obstetrics and Gynecology (ACOG) and the Society for Maternal-Fetal Medicine (SMFM), there is more awareness of the value of cfDNA NIPT. Genetic counselors, medical geneticists, and maternal-fetal medicine specialists, as well as primary care physicians, like obstetricians, are going to become very familiar with cfDNA NIPT in the coming years.

References

Learn more about the Illumina product mentioned in this article: verifi Prenatal test, www.illumina.com/clinical/reproductive-genetic-health/healthcare-professionals/non-invasive-prenatal-testing.html
THE VERIFI TEST WAS DEVELOPED BY, AND ITS PERFORMANCE CHARACTERISTICS WERE DETERMINED BY VERINATA HEALTH, INC. (VHI), A WHOLLY OWNED SUBSIDIARY OF ILLUMINA, INC. THE VHI LABORATORY IS CAP-ACCREDITED AND CERTIFIED UNDER THE CLINICAL LABORATORY IMPROVEMENT AMENDMENTS (CLIA) AS QUALIFIED TO PERFORM HIGH COMPLEXITY CLINICAL LABORATORY TESTING. IT HAS NOT BEEN CLEARED OR APPROVED BY THE U.S. FOOD AND DRUG ADMINISTRATION.