Impact of NIPT on prenatal screening for chromosomal anomalies

Prof. Dr. Bernd Eiben discusses advances in prenatal testing in Germany and his experience with the VeriSeq™ NIPT Solution v2

Introduction

During fetal development, normal cell turnover in the placenta results in a small fraction of cell-free DNA (cfDNA) circulating in the pregnant mother's blood. This cfDNA can be collected with a simple blood draw and analyzed with next-generation sequencing (NGS) to check for fetal chromosomal abnormalities. This noninvasive prenatal test (NIPT) can help patients and gynecologists avoid invasive amniocentesis or chorionic villus sampling by providing more accurate initial screenings.

Prof. Dr. Bernd Eiben heads prenatal screening at the amedes Group, a medical diagnostic service provider in Germany with a strong focus on gynecology and endocrinology. He is also a founding member of the Fetal Medicine Foundation in Germany. Prof. Eiben has been involved in prenatal genetic screening since 1984 and has witnessed the evolution of testing methods firsthand. He is a strong advocate for accurate, informative screening procedures that are focused on the needs and safety of pregnant mothers. His recent work at amedes includes extensive evaluation of the effectiveness of NIPT to support pregnant mothers and gynecology practices.

We spoke with Prof. Eiben about how he and his team are working with gynecologists and obstetricians to provide NIPT services and how amedes uses the Illumina VeriSeq NIPT Solution v2 as part of their service. We also discussed how policies in Germany around genetic testing impact prenatal screening options for pregnant women.
Interview

Q: What were the clinical and business factors that led to amedes offering NIPT in its portfolio?

Prof. Bernd Eiben (BE): amedes has always had a very strong focus on gynecology. With our robust genetic testing service, it was almost inevitable that we would be involved with NIPT. In our experience, it is very helpful for pregnant women to receive the clearest possible information from their prenatal test while avoiding unnecessary risks. The primary goal for us is always the well-being of the pregnant woman and the unborn child.

Q: Why did you decide to include NIPT in the amedes test offerings?

BE: NIPT has always played a special role in our approach to prenatal testing. We simply see it as our duty to help our colleagues in private practice by offering a good overall service. Gynecologists want information that is as clear as possible. This is important for selecting the ideal pregnancy management strategy.

The decision to order NIPT, and the potential changes in pregnancy management, must be made in close cooperation between the doctor and the pregnant woman. Every woman’s right to self-determination is of paramount importance. amedes supports this approach by providing clear information. For most pregnant women, NIPT provides a clear and reliable result based on robust and reliable data. They can better assess their situation and, if necessary, address any existing uncertainties with their doctor. In most cases, the NIPT results are reassuring for a pregnant woman.

Q: How did gynecologists initially react when you first started offering NIPT?

BE: There was no resistance. In fact, it may be more accurate to say that for a more technically savvy part of the gynecological community, providing an NIPT option was an important goal. That being said, a lot of people couldn’t believe that so much could be learned from a maternal blood draw, where previously the only options that were available have been invasive procedures such as amniocentesis or chorionic villus sampling. There were also some gynecologists who were skeptical at first and wondered whether the testing power that we promised was anchored in reality.
Q: Would you say that the expectations or aspirations of individual gynecologists have changed over time?

BE: Yes, even if you start off with first trimester screening, these are quite sensational innovations taking place. Over the past 20 years, awareness of these noninvasive test systems has become far more widespread, even amongst the public. This matter has very much occupied the minds of the gynecological community, as well as the regular press.

Progress in noninvasive testing has led to a significant decline of invasive prenatal testing, such as chorionic villus sampling or amniocentesis. According to published studies, this decline is up to 90 percent and has led to a collapse in these invasive tests. In this case, other advances are certainly significant factors, including improvement in ultrasound, first trimester screening, and now NIPT.

In the beginning, many were skeptical of NIPT as there had been talk of a regulatory frenzy. In Germany, the Genetic Diagnostics Act regulates the use of genetic tests for any medical purposes. Additionally, clinicians need to acquire specific certificates for genetic counseling in order to be able to offer certain tests. These certificates are not directly related to doing the test itself but are required to do the counseling related to the test. At amedes, we try very hard to keep these qualification measures in mind and aid clinicians in acquiring qualifications by offering the official courses required.

Q: Where does the gynecologist really see the benefit for ordering NIPT?

BE: The gynecologist, of course, is driven by the desire to give optimal prenatal care to the pregnant women. Also, most pregnant women, naturally, would like to deliver a healthy child. Progress in prenatal ultrasound over the last 20 years has led to a certain degree of expectations from many pregnant women. Due to improved screening, we can now move away from pure probability risk analysis and can be far more precise with it.

How results are conveyed is also important. We cannot say “there is a risk here,” but we should say “we must investigate this further.” For most pregnant women and gynecologists, the meaning of the test is much clearer now, and NIPT is gaining popularity amongst gynecologists. In general, it has already become established and it will continue to prevail and become an essential part of first trimester screening.
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Q: Can you explain how NIPT is offered and reimbursed in Germany today?

BE: NIPT has become a key offering for prenatal aneuploidy screening in Germany. In recent years, there have been negotiations to establish reimbursement by the public sector for NIPT and, in 2019, the Federal Joint Committee finally decided to reimburse NIPT, which is anticipated to begin in 2022.

Q: In some countries, NIPT is generally recommended as a primary test that can be offered to all women regardless of their risk. What is your view regarding primary use of NIPT?

BE: Sooner or later, I think that NIPT will become an important option for most pregnant women. But, the importance of prior genetic counseling must be emphasized. I am a big fan of the German Genetic Diagnostics Act, which makes such counseling mandatory.

Q: Can you explain your decision to adopt the Illumina VeriSeq NIPT Solution v2?

BE: Over the last 10 years, we have observed the evolution of NIPT technology. Many of the NIPT platforms have evolved technically and are now state-of-the-art. For example, we see how long processing times were in the past and how fast processing times are now. However, other platforms could not develop further, so the technology has essentially moved away from these. At the moment, I consider the VeriSeq NIPT Solution v2 to be the most advanced platform available. The reason for this is found in the PCR-free procedure, which naturally allows a very fast processing time of approximately one day. I believe that this is the fastest procedure available now. It was also very important for us to be able to reliably determine the fetal fraction and Illumina, in particular, has made considerable improvements to the whole process.

Another thing that was important was the implementation process. For both the original VeriSeq NIPT Solution v1 and the VeriSeq NIPT Solution v2, the test implementation into our laboratory workflow went really well, also quickly. I’d like to say many thanks to the whole implementation team at Illumina. They really did a very good job.
Q: Does the dynamic cutoff of VeriSeq NIPT Solution v2 have an impact on robustness and failure rates?

BE: It is particularly noteworthy that the improved focus on fetal fraction in VeriSeq NIPT Solution v2 resolved the inconsistencies that we previously observed. Due to the dynamic fetal fraction cutoff, we can now evaluate NIPT samples that contain a very small amount of placental DNA. Fortunately, we rarely have samples failing due to a fetal fraction below 4% in our lab. Therefore, for us, this new v2 solution is generally a very reliable tool with an extremely low failure rate, currently around 0.4%. That failure rate is also quite low in comparison to other NIPT platforms that we’ve had before and it is sensational in my eyes. This means we can provide findings with confidence to 99.6% of pregnant women.

Also, our turnaround time from receiving the sample to reporting the results is only around four days. This is important as it means that we typically have positive news for the pregnant woman in a short amount of time. That is a fact that we’re very pleased about.

Q: You recently published findings from your experience using VeriSeq NIPT Solution v2. What were the objectives of these studies and what were the most important conclusions?

BE: What we reported in these publications exemplified real-life medical practice and I think that’s a very important thing. We reported on over 41,600 NIPT samples, in total. Looking at the patients and the data, we concluded that most of the examined samples came from a normal population encompassing all risk levels. However, the composition of the general population has changed in Germany. Women are giving birth later in life with the average age of childbirth around 33 years, and that has moved upwards quite rapidly over the last 10 to 20 years.

We focused on the pregnancies where we found a high risk for trisomy 13, 18, 21, or monosomy X. In total, we had 545 cases that we tracked. We received clinical follow-up information in almost 83% of the cases with high-risk NIPT results. Overall, in this cohort that included 83% follow-up of abnormal NIPT result cases and 16% follow-up of normal NIPT result cases sensitivity and specificity were well above 99%.

These numbers are great, but they are not the most important values. The positive predictive value (PPV) is more important for pregnant women. PPV indicates the probability that a positive NIPT result truly represents the clinical reality. In other words, something that’s also confirmed in the fetus. The PPV depends on a number of different parameters, and the most important variable is the prevalence of the disease. As prevalence increases, so does PPV. For example, if you compare a trisomy 21 with a trisomy 13, trisomy
21 has a much higher prevalence than trisomy 13. In this case, there is also a clear difference between the PPV. From our study data, you can see that the PPV for trisomy 21 is at 94.1% in a total of 335 cases. Trisomy 13 has a much lower PPV of 60.5%. Trisomy 18, at just under 81%, lies between them. Monosomy X is at 66% but, if you consider the reason for referral, it is understandable. If you take the classic initial indication of advanced maternal age, 35 years and over, we can see that the PPV for trisomy 21 is at 95% with NIPT. If we go to the group under 35, then it’s 84.4%. So, for the NIPT, there is quite an increase in PPV.

Q: Apart from the technology, how would you characterize the collaboration with Illumina?

BE: We have regular contact with people at Illumina, and I have to say that our discussions are definitely very constructive and positive. Everyone involved does their best because we all agree that the primary focus should be on the welfare of the pregnant woman and we put the emphasis on this shared goal.

Learn more


Intended use statement

The VeriSeq NIPT Solution v2 is an in vitro diagnostic test intended for use as a screening test for the detection of genome-wide fetal genetic anomalies from maternal peripheral whole blood specimens in pregnant women of at least 10 weeks gestation. VeriSeq NIPT Solution v2 uses whole-genome sequencing to detect partial duplications and deletions for all autosomes and aneuploidy status for all chromosomes. The test offers an option to request the reporting of sex chromosome aneuploidy (SCA). This product must not be used as the sole basis for diagnosis or other pregnancy management decisions. Noninvasive prenatal testing (NIPT) based on cell-free DNA analysis from maternal blood is a screening test; it is not diagnostic. Further confirmatory testing is necessary prior to making any irreversible pregnancy decision.
References


