Advances in Screening for Genetic Abnormalities with Non-invasive Prenatal Testing

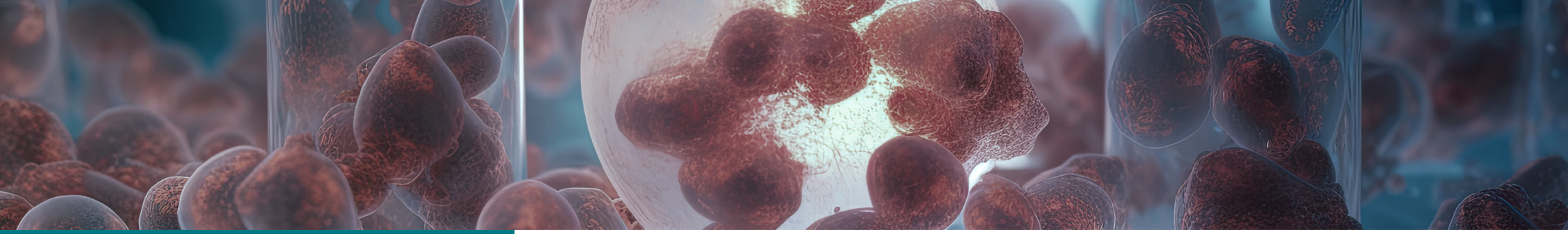
PD Dr Markus Stumm

FEBRUARY 2025

doi.org/10.33548/SCIENTIA1174

MEDICAL & HEALTH SCIENCES

Scientia



Advances in Screening for Genetic Abnormalities with Non-invasive Prenatal Testing

Non-invasive prenatal testing (NIPT) is a method of screening for genetic abnormalities in the unborn child through a simple blood sample taken from the mother. The non-invasive nature of the test has minimal to no risk to the mother and foetus and, since 2012, has been applied extensively around the world. As NIPT technology advances, Dr Markus Stumm of Medicover Genetics in Germany and his colleagues from Cyprus discuss the different techniques used, their strengths, their limitations and important considerations for pregnancy management.

What's in a Drop of Blood?

Non-invasive prenatal testing (NIPT) involves isolating cell-free DNA (cfDNA) from the plasma of a pregnant woman. This cfDNA consists of both maternal and so-called foetal components (placental origin), which circulate in the mother's blood. The percentage of foetal cfDNA in relation to the overall cfDNA circulating in the maternal plasma is called the foetal fraction.

Between weeks 10 and 20 of pregnancy, the foetal fraction equates to 10–15% of cfDNA (on average), meaning that screening for potential abnormalities can be done in the early phase of pregnancy. Dr Markus Stumm, Laboratory Head at Medicover Genetics, Berlin, Germany, explains that NIPT has become the first-line screening method for trisomies 13 (Patau syndrome), 18 (Edwards syndrome) and 21 (Down syndrome). In their 2022 review, the authors provide an update on NIPT use.

Underlying Scientific Rationale

Dr Stumm and colleagues discuss a number of available techniques that analyse cfDNA. We summarise two of these techniques here. Whole genome sequencing randomly sequences vast quantities of short cfDNA fragments in a genome-wide manner. This technology can be used to detect a number of different genetic anomalies but has some qualitative limitations.

In contrast, targeted technologies can only answer specific clinical questions but have specific qualitative advantages. One such technology developed by Medicover Genetics Cyprus is Target Capture Sequences – TACS. This technology uses long synthetic DNA probes specific to a select region of the genome. This allows for the enrichment of a smaller portion of the genome and thus avoids regions that are unnecessary and improves the precision and accuracy of the test. Another advantage of TACS is that it provides a very high level of read depth since the targeted region is smaller. This improves the statistical accuracy as well as the sensitivity and specificity of the analysis. The method also allows for multiplexing and an accurate foetal fraction estimate using proprietary bioinformatics software. A number of abnormalities can be tested using TACS including trisomies 21, 13 and 18, sex chromosome aneuploidies (SCAs) and certain microdeletion syndromes.

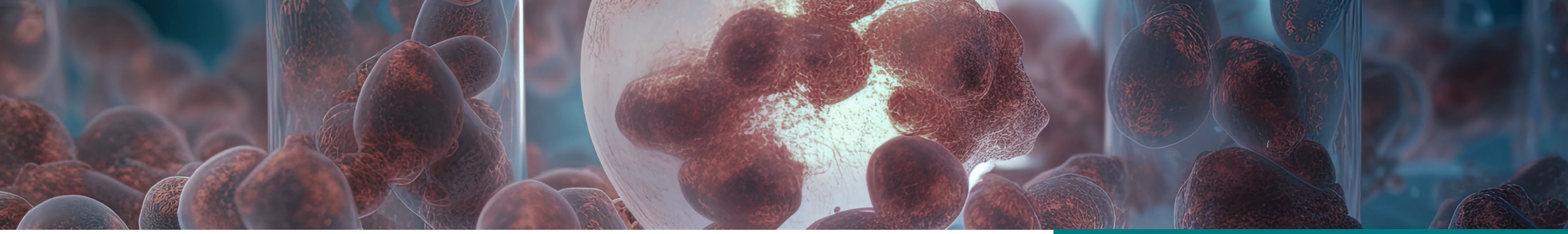
How to Implement and Manage Testing

Dr Stumm and colleagues explain that testing for common chromosome anomalies can be highly reliable. However, while advances allow for the testing of rare autosomal aneuploidies as well as microdeletions and microduplications, data are more limited in terms of the clinical significance of these outcomes. A number of factors can play a critical role, and as such, opinions on additional testing are currently divided among experts.

Structural abnormalities of chromosomes are another anomaly that NIPT can identify, but again, the clinical significance is debatable. Dr Stumm shares that although NIPT has the potential to address many genetic queries, when implemented a screening procedure, it must be critically evaluated. He adds, 'Every additional test option leads to a cumulative increase in the false positive rate and thus also a reduction in specificity'.

Practical Considerations for Clinicians

The foetal fraction is a very important factor for the accuracy of the NIPT, and the threshold for foetal fractions varies between methods. Dr Stumm recommends that laboratories optimise their estimation methods, implement robust quality assurance, and participate in external auditing schemes for the entire analytical process to ensure this.



Clinicians should be able to understand the factors influencing foetal fractions. When results are inconclusive due to low foetal fraction, they should be prepared to provide post-test counselling and consider re-collection of blood at a later stage of pregnancy or opt for invasive diagnostic testing such as amniocentesis. Because there are important clinical implications of no-call results due to low foetal fraction, Dr Stumm emphasises that it is important that the technology used for the tests should be one that accurately measures the foetal fraction percentage in order for the clinician to make the correct recommendation.

Discordance between NIPT results can be due to a number of reasons, including foetal-placental discrepancies and vanishing twin pregnancies. The vanishing twin syndrome is when one embryo in a gestation dies, and only one survives. This makes result interpretation difficult since the cfDNA from the vanished embryo is still detectable, which leads to a false positive result (if the vanished embryo had a genetic anomaly). Dr Stumm highlights that further clinical studies monitoring vanished twin pregnancies are required.

Planning for Screening

Dr Stumm shares that a baseline sonogram can provide important information and should be done before testing. Since cfDNA analysis is the most sensitive and specific test for common genetic anomalies, it should be offered to all women. Performed at 10 weeks of pregnancy as the first line test, the analysis and follow-up can then be completed in the first trimester, and in the case of failed tests, follow-up ultrasound screening can be done in a timely manner. Mothers with positive test results should always be offered direct genetic counselling and the options for invasive diagnostic testing.

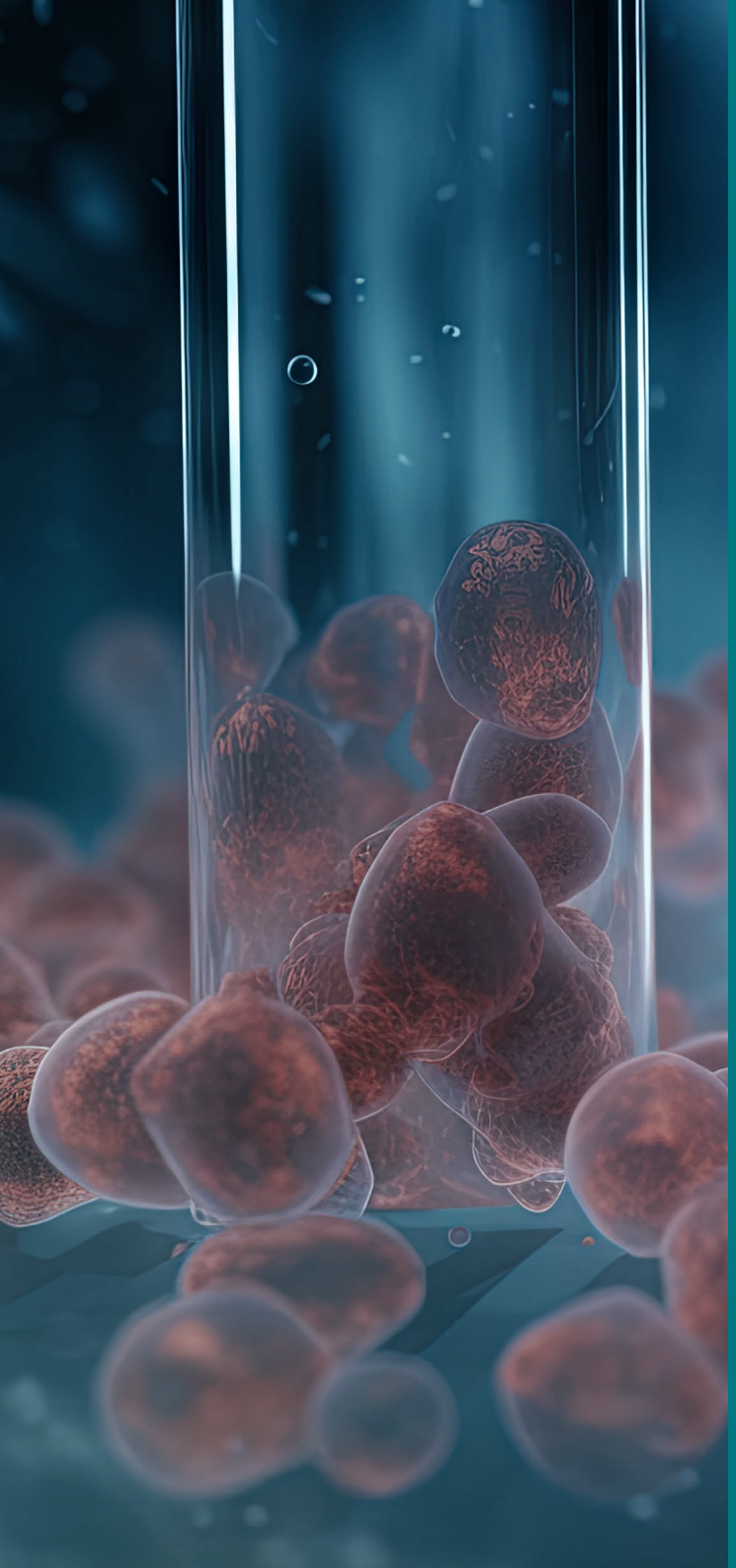
An alternative suggested by Dr Stumm is to offer NIPT as contingent screening to women with an increased aneuploidy risk based on the results of the first-trimester screening. This method increases the detection rate and decreases the false positive rate. However, one disadvantage to this approach is that the diagnoses may be shifted to the second trimester for those with failed tests.

With regard to genetic counselling, Dr Stumm believes that pregnant women should make informed choices about screening and diagnostic testing. They should understand the advantages and limitations of these tests, and this needs to be clearly explained to patients. Furthermore, counselling should be provided to them in regard to their specific risk. Following the retrieval of results, the post-test counselling should clearly explain the test results and next steps. An important point expressed by Dr Stumm is that 'patients with negative test results should be made aware that the test result only decreases the risk for the tested conditions but does not ensure that the foetus is healthy'.

Next Steps

Though there are different technological advancements in NIPT, all having their own strengths and limitations, there is a need for careful result interpretation with appropriate counselling and clinical management. Despite this, NIPT has revolutionised prenatal screening and is currently the most effective screening test for trisomies 13, 18 and 21. Dr Stumm concludes, 'With further technological advances and responsible innovation, NIPT remain a screening avenue for the detection of additional genetic conditions'.

> Dr Stumm believes that pregnant women should make informed choices about screening and diagnostic testing.



MEET THE RESEARCHER

PD Dr Markus Stumm
Medicover Genetics, Berlin, Germany

Markus Stumm received his PhD in Human Genetics from the Free University Berlin in 1997. At present, he serves as the Laboratory Head at Medicover Genetics, Berlin. Over the years, his research has focused on medical genetics, cytogenetics and diagnostics, with a specialist interest in prenatal diagnosis. He has published extensively in his field.

CONTACT

markus.stumm@medicover.de
https://www.researchgate.net/profile/Markus-Stumm
PD Dr. rer.nat. Markus Stumm

MEDICOVER
GENETICS

KEY COLLABORATORS

Medicover MVZ Martinsried GmbH

Medicover Genetics Cyprus

FURTHER READING

E Kypri, *et al.*, Non-invasive prenatal screening tests – update 2022, *Journal of Laboratory Medicine*, 2022, 46(4), 311–320.
DOI: https://doi.org/10.1515/labmed-2022-0023