Non-Invasive Prenatal Test (NIPT)

azdelta

Content

Dear Expectant Parent,

As a pregnant woman, close follow-up by your gynaecologist is very important. Your physician will monitor your health and the baby's health through physical examination, blood- and urine tests and ultrasound imaging.

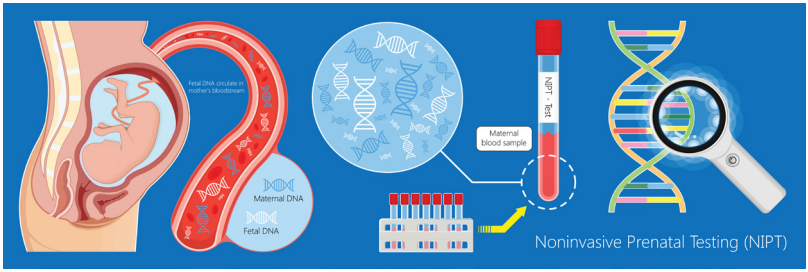
You have the option to have your unborn baby screened for various birth defects or pregnancy-associated risks; this is called prenatal screening. The cornerstone of prenatal screening includes sonography and, more recently, also Non-Invasive Prenatal Testing (NIPT) for screening of Down syndrome (trisomy 21) and other chromosomal abnormalities in the baby.

Currently, all pregnant women in Belgium can have NIPT for Down screening reimbursed by national healthcare from gestational week 12. In this brochure we will provide you with clear information to help you make a well-informed decision. We will discuss the underlying technology of whole-genome NIPT sequencing, its potential benefits and its limitations. More importantly, we will highlight the various possible outcomes of NIPT and how these could affect your pregnancy. If you have any remaining questions, please feel free to contact the laboratory or ask your gynaecologist.

Sincerely,

Department of Laboratory Medicine, AZ Delta general hospital

How does NIPT work?



The NIPT is performed using a blood sample from the mother. Human blood contains small pieces of DNA, which are random fragments from the various chromosomes that carry our genetic code. This DNA comes from the normal turnover of cells in the body. In the blood of pregnant women, approximately 5% to 10% of this circulating DNA comes from the placenta. The placenta contains a mixture of cells from both the mother and the fetus, and therefore, its DNA is usually representative of the fetus's DNA. This is why it is generally referred to as "fetal DNA"

Your NIPT test will be done using the **VeriSeq™ NIPT test** (Illumina, USA). This test uses a technology called 'shallow genome-wide (or whole genome) sequencing'. The term 'whole-genome DNA analysis can cause some confusion. Many people assume that in the process of a whole-genome NIPT, the complete DNA code of the mother and fetus is accurately analysed, thus potentially revealing all possible DNA defects. However, this is not the case. Instead, the test reads very small DNA fragments, randomly distributed across all human chromosomes.

If the fetus has a significant anomaly, such as an extra copy of chromosome 21, the test will detect clearly more fragments of that specific chromosome than of the other chromosomes. This leads to a screening result positive for trisomy 21, also known as Down syndrome. Similarly, the test can also detect an extra copy of other chromosomes, such as chromosome 13 or 18, or changes in the number of sex chromosomes (X and Y). Because whole-

genome NIPT measures the copy number of all chromosomes, abnormalities in other chromosomes can also be detected incidentally. These are called '**incidental findings**,' and you will learn more about their importance later in this brochure

Conditions routinely screened by VeriSeq™ NIPT test

NIPT is reimbursed in Belgium specifically for the screening of **Down syndrome (trisomy 21)**. All NIPT tests available in Belgium also screen for **trisomy 18 (Edwards syndrome)** and **trisomy 13 (Patau syndrome)**. The VeriSeq NIPT test additionally carries a CE-IVD mark for screening for **anomalies of the sex chromosomes X and Y**, but it this is optional.

Down syndrome (trisomy 21) is a primary cause of intellectual disability. Trisomy 21 is a genetic condition where the baby has three copies of chromosome 21 instead of the usual two. The risk increases sharply with the mother's age: under 30, the risk is less than 1 in 1000, but at age 35, it increases to 1 in 350. Nevertheless, most children with Down syndrome are born to younger women, as they make up the majority of births. The severity of intellectual disability varies and cannot be predicted by NIPT. How parents experience having a child with Down syndrome is very individual, and many parents of children with Down syndrome are very happy with their child. Therefore, the choice to screen is entirely personal.

Edwards syndrome is a very serious abnormality caused by an extra copy of chromosome 18 (**trisomy 18**). Most babies with trisomy 18 die during pregnancy or shortly after birth. They typically have severe defects in the brain, heart and other organs which can usually be detected using sonography. It is a rare condition, affecting 1 in 10,000 pregnancies.

Patau syndrome is caused by an extra copy of chromosome 13 (**trisomy 13**). Like trisomy 18, it is very rare (1 in 10,000 pregnancies) and very severe, with most babies dying during pregnancy or shortly after birth.

How reliable is NIPT?

It is important to understand that **NIPT is a screening test, not a diagnostic test**.

A screening test is developed to achieve a maximal sensitivity. The VeriSeq NIPT test achieves a sensitivity close to 100%. Based on our own data on more than 30,000 NIPT screenings from 2018-2022 (1), not a single case of trisomy 21, 18 and 13 was missed. This does mean that in very rare cases the VeriSeq NIPT can miss cases (2,3), but the odds of such a '**false negative**' screening are very limited.

The downside of such an extremely sensitive screening, is that the test can also generate '**false positive'** screening results. In these cases, NIPT suggests the presence of a chromosomal defect, but analysis of the fetus's DNA shows a normal makeup. The main cause of such false positive results, is that the chromosomal error detected by NIPT is confined only to the cells of the placenta, from which the circulating fetal DNA derives. This situation is scientifically referred to as **Confined Placental Mosaicism (CPM)**, which we will discuss this later.

What truly matters, of course, is the genetic status of your child. Therefore, if you receive an abnormal NIPT result, you will be offered follow-up testing through amniotic puncture. In this procedure, amniotic fluid is collected, and fetal cells in this fluid are analyzed using an independent method for chromosome defects. Amniotic puncture is not risk-free: in 2 out of 1000 cases, such a puncture can lead to pregnancy loss. You have the right to refuse this procedure. The puncture can be performed

from pregnancy week 15 onwards, typically two weeks after receiving the NIPT result. The amniotic puncture provides 100% certainty and is therefore a truly diagnostic test.

For VeriSeq™ NIPT results suggestive of trisomy 21, around 25% are not confirmed by the subsequent puncture, and the fetus will develop normally. Medical NIPT specialists have access to advanced digital tools to recognize likely false positives due to placental mosaicism. They will provide this information to you and your gynaecologist to help reduce anxiety in preparation for the amniotic fluid examination.

Determining the fetal sex

VeriSeq NIPT also measures fragments of the X and Y chromosomes in the mother's blood. These chromosomes determine the sex of the child: girls have two X chromosomes (XX), while boys have one X and one Y chromosome (XY). The mother typically has two X chromosomes. Mothers carrying a male baby will thus show fragments of the fetal Y chromosome in their blood, while the absence of a Y chromosome in the mother's blood indicates a female baby. This way, the baby's sex can be correctly identified in at least 99% of cases.

The baby's sex is **always measured, but by default, it is NOT reported to you**. Only if you explicitly choose to know the sex of the baby through the informed consent form will it be mentioned on the laboratory email report sent to the email address you provided. **Please note: for IT technical reasons, the baby's sex is always transmitted to digital health forms such as CoZo or mijn.azdelta. So, if you do not wish to know, please refrain from checking your NIPT result there.**

Abnormalities of the X- and Y-chromosomes in the baby

Unique to your VeriSeq NIPT is that this test also has European certification (CE-IVDR) for the screening of abnormalities in the number of X and Y chromosomes in the fetus. In these abnormalities, the baby has an extra copy of an X or Y chromosome, or has lost one X chromosome. The most important abnormalities are female babies with Turner syndrome and boys with Klinefelter syndrome. The actual sensitivity of VeriSeq NIPT to screen for these syndromes is not fully known. However, if the test suggests a baby with Turner syndrome, this is confirmed in 50% of cases in the fetus. For Klinefelter syndrome, 89% of cases are confirmed (1).

Abnormalities of the sex chromosomes **are always measured by VeriSeq NIPT, but by default, they are NOT reported to you.** Only if you explicitly choose to be informed about X or Y abnormalities through the informed consent form will you be contacted by your physician for further counseling or follow-up testing. Counseling is very important for these disorders, as in most cases, they do not present a medical reason for pregnancy termination and can cause emotional stress for the parents. To help you make a well-informed decision, we will summarize the main facts about these syndromes and their effect on the quality of life for the child and the parents below.

The Klinefelter syndrome

Klinefelter syndrome occurs in male babies who have one or more extra copies of the X chromosome. Instead of the normal 46 chromosomes—including one X and one Y chromosome (46, XY)—boys with Klinefelter syndrome have two X chromosomes (47, XXY) or even three X chromosomes (48, XXXY). This abnormality occurs in approximately 1 out of 850 male births.

During childhood, the syndrome largely goes unnoticed as there

are virtually no symptoms, so the majority of XXY men never receive a diagnosis. Due to the extra X chromosome, boys with Klinefelter often develop a larger stature. More importantly, they may have problems with hormonal development, leading to delayed puberty, decreased libido, and often infertility due to a lack of testosterone. Therefore, the diagnosis today is typically delayed until puberty or when men seek medical help for reproductive issues. At puberty, boys with Klinefelter may experience feeling different, leading to social problems or difficulties at school, despite having perfectly normal intelligence.

The advantage of NIPT screening and knowing the diagnosis earlier is that parents can seek preventive help, for instance, through early hormone therapy around puberty. The disadvantage of screening is the emotional stress and anxiety for parents about not having the 'perfect' child. Opinions are clearly mixed, and the choice is highly individual: prior experience shows that half of parents who received a positive screening for Klinefelter were happy to be prepared, but the other half regretted screening because they experienced stress during pregnancy at the prospect of having a boy with a possible vulnerability.

Please note that in Belgium, Klinefelter is not a medically accepted condition for termination of pregnancy. So, before making this choice, please consider this screening carefully. You can find good online information from patient groups such as livingwithxxy.org and Klinefelter's Syndrome Association (www.ksa-uk.net), among others.

Turner syndrome

Turner syndrome develops in female babies who lack one X chromosome. Instead of the normal 46 chromosomes with two X chromosomes (46, XX), girls with Turner syndrome have only 45 chromosomes with one X chromosome (45, X0). The severity of Turner syndrome varies widely. In some cases, fetuses with Turner syndrome already show severe developmental

abnormalities around 12 weeks of gestation, which can be a possible indication for termination of pregnancy. In the majority of cases, however, the fetus appears to develop normally.

One reason for this variation in severity is that Turner syndrome can be characterized by what is called 'fetal mosaicism,' meaning that only a fraction of the fetal cells are affected by the loss of an X chromosome. Many women with such 'mosaic Turner syndrome' live normal, healthy lives and have children. When all fetal cells are affected (non-mosaic Turner), the syndrome can be more symptomatic: this classical non-mosaic Turner syndrome affects 1 out of 2000 female births.

The lack of one X chromosome can cause variable physical signs such as shorter stature, mild abnormalities in the physical appearance of eyes, ears, neck, and chest, and (mostly in babies) swollen feet and hands. Girls with Turner syndrome have a higher chance of heart and kidney defects. But the most important manifestation is problems with hormonal development: besides lower thyroid function, Turner patients experience problems with ovarian function. Girls with Turner syndrome produce insufficient female hormones (estrogen), leading to delayed menstruation and frequent infertility. Starting early with hormone therapy (toddler age) can prevent some of these symptoms: growth hormone therapy can result in a larger stature, and estrogen therapy can help sexual development.

Screening for Turner syndrome by NIPT is a relatively new technological option, so we currently have limited knowledge about the experiences of mothers who received a screen-positive Turner result. There is also a disparity in medical and ethical opinions, though most medical professionals agree that early screening of severe Turner cases is valuable. As with Klinefelter syndrome, it is important that you, as a future parent, seek good information. There are many patient associations that can help you, such as www.turnersyndrome.org, turnersyndromefoundation.org, and others.

Other benign variations: Triple X syndrome and XYY

Triple X syndrome is not truly a disease: it occurs in girls with an extra copy of the X chromosome. This can cause a somewhat larger stature but generally leads to perfectly normal development. It occurs in 1 out of 1000 female births. Another variation is boys with one extra Y chromosome copy (47, XYY). This was originally referred to as Jacobs syndrome, but we now know that this extra Y chromosome does not affect development. Therefore, even though VeriSeq NIPT can accurately screen these traits, they will not be reported to you.

Incidental findings of genome-wide NIPT

Since VeriSeq is a genome-wide NIPT assay, it can also detect abnormalities of chromosomes other than 13, 18, 21, X, and Y. As NIPT was not developed to screen for such rare anomalies, they are referred to as 'incidental findings'. The significance of these incidental findings for the pregnancy is not always clear. Sometimes they can cause a miscarriage early in the pregnancy. Sometimes these abnormalities are only present in the placenta, but not in the baby. Very rarely, such incidental findings can also indicate a problem in the mother's DNA: approximately one out of 5000 NIPT tests accidentally reveals the presence of cancer in the mother, where abnormal tumor DNA triggers an abnormal NIPT result. If such incidental findings are detected and are considered important for the course of the pregnancy, you will be informed by your gynaecologist, and tailored follow-up examinations will be proposed. Receiving such a result can be confusing and difficult to understand. Therefore, you will also be offered genetic counseling and psychological support by our teams.

Overall, these incidental findings can be broadly summarized

in **3 different types**:

- Rare Autosomal Trisomies (RAT): In these cases, NIPT shows the presence of one additional copy of a numbered chromosome (autosome) other than 13, 18, or 21. This occurs in 3 per 1000 NIPT screenings. The least rare is Trisomy 7 (+7). In most cases, an additional copy of such a chromosome is not compatible with a viable fetus. As a consequence, cases screened by NIPT at 12 weeks gestation typically involve Confined Placental Mosaicism (CPM). Virtually 100% of trisomy 7 positive screenings are not confirmed by amniocentesis, simply because only the placental cells are affected, and the fetus is normal. As a group, these RATs are confirmed in only 6% of amniocenteses. For some RATs (e.g., trisomy 14, 15, or 16), the risk is much higher. Therefore, the NIPT specialist will issue a tailored recommendation for amniocentesis only if needed. We do know, however, that even if the RAT is confined to the placenta, there is a risk for your pregnancy: an extra chromosome copy in the placenta can negatively affect the normal function of the placenta (oxygen and nutrient delivery from mother to fetus). So, even if the defect is not confirmed in your fetus, your gynaecologist will propose closer follow-up of your baby's growth through sonographic monitoring.

- **Microduplications or microdeletions**: sometimes the gain or loss does not affect a complete chromosome, but only a segment of it. VeriSeq NIPT can detect such microduplications or microdeletions when they are at least 7.5 million DNA letters. If your fetus has such a sub-chromosomal defect, and important genes are lost or multiplied, there is a risk for developmental issues. These anomalies occur in 2 out of 1000 NIPT screenings. We will always propose an amniocentesis, and the fetal defect is confirmed in 40% of cases.

- **Complex profiles with multiple chromosomal abnormalities**: these are very rare (1 in 2000 NIPT screenings), but are always considered a trigger for amniocentesis. In 33% of cases, these abnormalities are confirmed in the fetus. In the

remaining cases, such profile can indicate the presence of an unrecognized cancer in the mother (mostly of blood cells). Therefore, your physician will certainly run additional tests to be sure.

Screening for cytomegalovirus infections by NIPT

The **cytomegalovirus (CMV, HHV-5)** is a common virus from the Herpes family. In healthy adults, it causes a transient and mild flu-like syndrome. However, if the infection occurs in the **first trimester** of pregnancy and the mother is not immune, there is a **35% risk that the CMV virus will be transmitted** through the placenta from mother to fetus. The developing nervous system of the first-trimester fetus is very susceptible and can be damaged, leading to **hearing loss** and other defects. An infection later in pregnancy carries much less risk for fetal damage. This is a prevalent and often overlooked problem: **7 in 1000 babies are born with a CMV infection** (congenital CMV), and at least 20% of these newborns will go on to develop lifelong hearing loss. Pregnant mothers who have frequent contact with infants, for example, with a prior child in day-care, and who have no prior immunity (antibodies in blood) to CMV, are most at risk.

Screening for first-trimester primary CMV infection is possible through so-called **serological assays**: in this case, a routine lab measures the presence of antibodies to the CMV virus in the blood. Subjects with no antibodies ('seronegatives') are considered non-immune and susceptible, and these subjects are then monitored for the appearance of CMV antibodies throughout pregnancy. In most parts of the world, such serology-based CMV screening is not supported by medical professionals for two reasons. First, because serology-based screening has many limitations (false negatives and false positives). Second, and most importantly, because there was no cure if a CMV infection

was found. This has now changed, with recent studies showing that the **risk for transmission from mother to child can be reduced by 70% with antiviral therapy (valacyclovir)**(4). To date, this preventive therapy is not yet reimbursed in Belgium, even though it has been proven safe and effective.

To support awareness about CMV and to improve universal screening, the AZ Delta laboratories developed **a novel and complementary way of screening for CMV infection by detection CMV viral DNA fragments in the NIPT test** (5). In short: during NIPT, we analyse millions of small DNA fragments circulating in the mother's blood. A very small fraction (<0.1%) of these DNA fragments are not human-derived but come specifically from DNA viruses. So, we re-utilize the DNA data captured during your NIPT, and with only computer power, we can detect and even quantify the amount of circulating viral DNA. This way, we can screen for active infections by CMV and other viruses such as Parvovirus B19, Hepatitis B, and various Herpes viruses. To enable timely access to preventive antiviral therapy, we decided to implement this scheme with a focus on CMV and perform this analysis on all NIPTs. To support this program, we charge a **personal contribution of 12.50 euro** simply to cover computing costs. Using this tool, an increased number of CMV DNA fragments can predict the risk for congenital CMV infection, with positive predictive values above 50%.

If your NIPT shows a CMV infection, you and your gynaecologist will receive a tailored recommendation for follow-up testing (serology), depending on the number of viral particles, and together we will decide if antiviral therapy is indicated.

NIPT does not detect all DNA defects

NIPT technology was developed to screen for large DNA defects,

such as the extra copy or loss of an entire chromosome. Most common hereditary diseases (e.g., cystic fibrosis or haemophilia) are not caused by such large defects, but rather by very small errors in the genetic code. NIPT cannot detect such small errors that occur in what are called monogenic diseases.

If you are aware of **genetic diseases in your family** or if you suspect such diseases, please **inform your gynaecologist** and have this mentioned on the NIPT test request form to inform the laboratory specialist. Your gynaecologist can refer you to a **genetic counsellor** to decide if more specialized DNA tests are mandatory. This can range from a broad genetic screening of the DNA of the mother and the father (**carrier screening**) for hundreds of known monogenic diseases, to a highly targeted DNA test of one suspect gene in the parents or in the baby.

A well-informed personal choice

NIPT is reimbursed for all women in Belgium, but the choice to undergo it is yours. Also, if you decide not to use NIPT screening, your pregnancy will be adequately monitored and in case of abnormal sonography results, you still have access to further amniotic puncture testing. So before taking the NIPT, ask yourself the following questions:

- *What if my NIPT is abnormal: will I opt for an amniotic puncture?*
- *If the amniotic puncture shows that my baby has Down syndrome, how will my partner and I deal with it?*
- *Shall we choose to continue to the pregnancy or do we consider an interruption?*
- *If I know that my baby has Klinefelter or Turner syndrome: won't I be unhappy and stressed?*
- *Do my partner and I share the same view on raising a child with Down syndrome or a mild syndrome like Turner and Klinefelter?*
- *Will I be unhappy knowing that my growing infant has a*

vulnerability such as Turner or Klinefelter?

Practical details

When?

NIPT is reimbursed only if the blood is sampled from **pregnancy week 12**. In principle it is technically possible from week 10, but the timing at week 12 was chosen because an eventual follow-up test through amniotic puncture can only be done from week 15 onwards.

What is the cost?

NIPT costs 265 euro and is almost completely reimbursed if you are covered by the Belgian health care system (RIZIV/INAMI). You only pay a personal contribution of 8.68 euro unless you meet the criteria for extensive support. NIPT done before pregnancy week 12 is NOT reimbursed and the full sum will be charged. For the default **screening of CMV viral infection** a bioinformatic fee of **12.5 euro** for computing cost is additionally requested, bringing total maximal **personal contribution at 21.18 euro**.

Informed consent

If you decide to undergo NIPT testing, your gynaecologist will complete the NIPT test request form. The front page of this form provides important information for proper test interpretation by the laboratory specialists. The back page consists of the informed consent form: you will need to sign this to confirm that you were properly informed about the potential benefits and limitations of NIPT, data sharing policy, and to indicate if you choose to be informed about the sex of the baby, and/or if you wish to be informed in case of abnormalities such as Turner syndrome or Klinefelter syndrome.

The blood draw

The blood draw will take place at AZ Delta hospital or at your physician's office. This requires a special collection tube that optimally preserves the fetal DNA. It is important to avoid physical efforts in the hour before the blood draw. Even medium-intensity exercise such as 20 min biking should be avoided since this can decrease the relative amount of fetal DNA in the blood, leading to NIPT failure.

When and how do I receive the result?

The NIPT result is available within 10 days after blood sampling. In approximately 1 out of 20 patients, the sample needs to be analysed twice in order to get a reliable result, causing a delay. If the test is normal, you will receive an email to the email address you provided on the informed consent form.

The NIPT result is available: what next?

In practice, NIPT testing can generate 3 outcomes:

In approximately 99 out of 100 women, NIPT shows a NORMAL result.

In that case, the risk for trisomy 13/18/21 is very low, and no follow-up testing is needed. You will receive the test report with the normal result by email.

In approximately 1 out of 100 women, NIPT shows an INCONCLUSIVE result.

In most cases, this is caused by a fetal fraction that is too low to allow conclusive testing. The fetal fraction is the proportion of DNA originating from the placenta, relative to the total DNA in the blood which is mostly composed of DNA from the mother. When the fetal fraction is too low, the NIPT analysis achieves insufficient sensitivity and no reliable assessment of fetal trisomies can be made. In most cases, a **low fetal fraction** is caused by an increased amount of DNA from the mother in her blood. This is often observed in case of:

- **Obesity** (BMI > 30)
- **Physical exercise** in the hour before blood sampling e.g. 20 minutes of biking
- Some other conditions (autoimmune diseases, psoriasis,) characterized by increased cell turnover

In some women, the low fetal fraction is caused by a lower amount of placental DNA for reasons unknown. If your first NIPT test gives an inconclusive result, you will be contacted by the lab for a new blood sample, and a repeat NIPT testing at no additional cost. In around 50% of the cases this repeat NIPT test also fails: in that situation, further NIPT testing is not

useful and your gynaecologist will discuss further options such as conventional biochemical screening.

In less than 1 out of 100 women, NIPT gives an ABNORMAL result

In this case you will be contacted by your gynaecologist, who will usually propose amniotic puncture for diagnostic testing. The abnormal NIPT result can be caused by abnormalities in:

- The baby: a NIPT result suggestive for trisomy 13, 18 and 21 is subsequently confirmed in respectively 17%, 70% and 75% of cases in the fetal cells.
- The placenta but not the baby: the DNA defects are limited to the placenta but the baby is healthy (CPM). In that case your gynaecologist will propose a close sonographic follow-up, or when medically required, an amniocentesis.
- The mother: rare cases of maternal cancer

An abnormal NIPT result causes a lot of anxiety and raises many new questions. Your gynaecologist will discuss further options including interruption of the pregnancy in case of trisomy 13/18/21, psychological support and access to a genetic counsellor who can provide more information on the severity of the disorder, and the possible impact on quality of life for parents and the baby. The AZ Delta hospital and the AZ Delta Medical Laboratories have a partnership with the Medical Genetics Department of University Hospital Gent. The counseling can take place in one of our AZ Delta network hospitals or at UZ Gent.

Privacy and data policy

AZ Delta Medical Laboratories are compliant with European GDPR (General Data Protection Regulation) for data storage and protection. Your DNA data will be stored safely and will

not be shared with third parties. Your DNA data and residual blood sample can be used after anonymization for research and development of diagnostic pipelines by AZ Delta and its scientific collaborators. NIPT results and outcome data are collected in a central database to monitor test quality (false/true positivity/negativity rate and incidental findings) in accordance with legal obligations of medical data recording.

The evolution of NIPT data analysis is continuously ongoing, and newly developed tools implemented on past data can provide relevant information on your health. Therefore, we ask for your permission in the Informed Consent form to contact you after birth, in case later re-analysis of your NIPT data suggests the occurrence of such anomalies and if outcome data are useful for proper interpretation. You will be contacted if the observed anomaly has demonstrated medical importance and after approval by the Ethical Committee.

Video

Watch the NIPT-video via this QR-code.

Scientific references

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5. Herroelen PH, Swaerts K, Descheemaeker P, Claerhout P, Vanderstichele A, Boone E, et al. Universal Screening of Cytomegalovirus Viral Load by Low-Pass Whole-Genome Sequencing in First-Trimester Pregnancy: Clinical Validation. Clin Chem 2025 Dec 30;72:1:173-82.

Contact

More info?
If you have any questions or remarks after reading this brochure, you can always talk to your gynaecologist or you can contact the Laboratory Medicine Department by email.

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