Information brochure for prospective parents

Non-invasive prenatal testing (NIPT)

Universitair Ziekenhuis Brussel

PERINATAAL CENTRUM Moeder en kind

Centrum voor Medische Genetica

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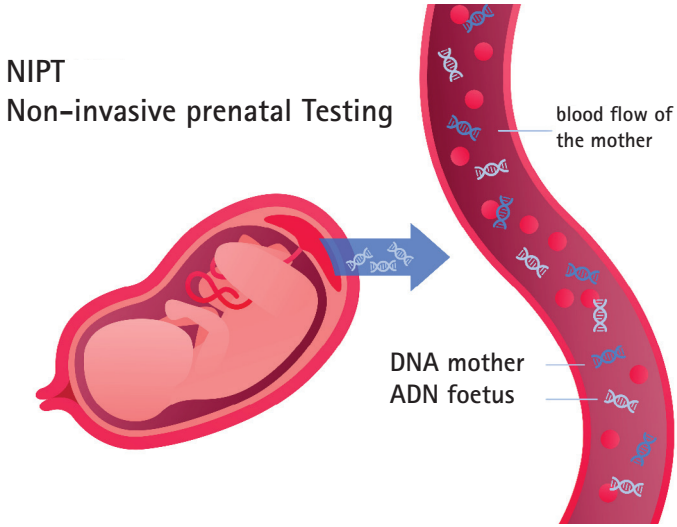
NON-INVASIVE PRENATAL TESTING (NIPT)

Non-Invasive Prenatal Testing (NIPT) is a screening technique developed specifically for the detection of Down syndrome (trisomy 21), Edwards syndrome (trisomy 18) and Patau syndrome (trisomy 13), see page 5. We examine the foetal DNA (hereditary material) that circulates in your blood. At UZ Brussel, NIPT is only done when you are 12 weeks pregnant, after an ultrasound.
It is entirely up to you whether you want to have NIPT done. During your first pregnancy consultation, we explain this testing technique to you and provide you with our information brochure. We ask that you take the time to read this brochure in advance. Do you still have questions about NIPT? We are happy to answer them before NIPT is performed.



1. HOW DOES NIPT WORK?

NIPT is a blood test that examines the foetal DNA (hereditary material) circulating in the mother's blood. Foetal DNA from the placenta is present in the mother's blood early on in the pregnancy. This is known as cell-free DNA or cfDNA. NIPT analyses how much of the DNA in the mother's blood came from the unborn child or foetus (foetal fraction) and the composition of this DNA. There is usually enough DNA present from the twelfth week of gestation to get a reliable result. For a maternal BMI (body mass index) above 30, we recommend performing NIPT from 14 weeks of gestation.

2. THE FIRST-TRIMESTER ULTRASOUND BEFORE NIPT

All pregnant women undergo a first-trimester ultrasound between the 11th and 14th week of gestation. We do this to check the unborn child's development as best we can. If we detect anomalies on the ultrasound, we recommend that you seek genetic counselling and a more targeted follow-up of your pregnancy. In that case, we also consider other diagnostic techniques to complement or replace NIPT.

3. PROS AND CONS OF NIPT

3.1 BENEFITS

NIPT provides a result with a blood sample from the mother only so there is no risk of miscarriage. With invasive tests, such as amniocentesis and chorionic villus sampling, there is a small risk (0.5 - 1%) of miscarriage.
NIPT has a sensitivity of more than 99% for detecting trisomy 21. This means that 99 of 100 babies with Down syndrome will be detected with this test. It is also a very good (sensitive) test for the two other common syndromes caused by chromosomal abnormalities, namely trisomy 18 and trisomy 13.
NIPT, as used in Belgian genetic centres, is a comprehensive screening test, in which we analyse the number of chromosomes in chromosomes 13, 18 and 21, as well as other chromosomal aberrations.

3.2 DISADVANTAGES

NIPT is a screening test, it doesn't diagnose conditions. An abnormal NIPT result should therefore always be confirmed by an invasive test, preferably amniocentesis.
NIPT can only diagnose major chromosomal abnormalities and is not suitable for detecting minor chromosomal abnormalities. This also requires an invasive test.
In less than 5% of cases, NIPT fails to provide a conclusive result, usually due to an insufficient amount of foetal DNA (foetal fraction) in the mother's blood or a poor quality sample.

4. WHAT DOES THE NIPT ANALYSE?

Most babies are healthy, but every baby has a small chance of being born with a physical and/or intellectual disability. In some cases, this is caused by an abnormality in the chromosomes, which are the carriers of our hereditary material.
Typically, people have 46 chromosomes. These chromosomes are divided into 23 pairs, half of which are inherited from the father and the other from the mother.
The 23rd pair of chromosomes determines the baby's sex: XX for a woman, XY for a man. Typically, each pair contains two chromosomes, a maternal and a paternal chromosome.

4.1 TRISOMY 21

A baby with trisomy 21 (also known as Down syndrome) has three separate copies of chromosome 21 instead of the normal two copies. People with trisomy 21 have 47 chromosomes instead of the typical 46. Trisomy 21 is the most common chromosomal abnormality. The main manifestations of trisomy 21 are mild to severe intellectual disability and specific facial features. There are also a number of other physical characteristics and conditions.

4.2 TRISOMY 13 and 18

Besides trisomy 21, other less common forms of trisomy (three copies) include trisomy 18 (Edwards syndrome) and trisomy 13 (Patau's syndrome). Both conditions are associated with severe congenital disorders, such as brain and other organ abnormalities, spina bifida, cleft lip/palate, with the child usually dying during pregnancy or shortly after birth. However, trisomies 13, 18 and 21 are potentially survivable chromosomal abnormalities.

4.3 SEX

NIPT can also determine the sex of your baby, but this is not the purpose of this technique. Moreover, sex determination is not 100% accurate, so we recommend confirming the baby's sex by ultrasound.

4.4 OTHER CHROMOSOMAL ANOMALIES

NIPT can detect other chromosomal aberrations besides trisomy 13, 18 and 21. If the anomaly is important for the health of the mother and/or child, this will be flagged in the screening report and discussed with you. There are guidelines for this from the Belgian College for Human Genetics and Rare Diseases (www.college-genetics.be).

4.5 SEX CHROMOSOME DISORDERS

NIPT can detect several sex chromosome disorders. Some of these do not pose a major health problem, while others affect both the child's physical and mental development, such as Turner syndrome and Klinefelter syndrome. Early detection of these disorders is important for treatment and prevention of possible complications.

You indicate in advance on the consent form whether you want to be informed about the possible detection of these two syndromes.

TURNER SYNDROME

Girls/women with Turner syndrome have 45 chromosomes instead of the usual 46. They are missing one X chromosome in a pair, which is why this syndrome is also known as 'monosomy X'. Girls with Turner syndrome usually look normal, but this may affect their growth in all phases of growth. They have a higher risk of:

- Congenital abnormalities of the heart and kidneys and lymphoedema (accumulation of lymph fluid).
- Ear infections with risk of hearing loss.
- A shorter stature than expected based on their parents' height.
- Ovarian dysfunction. Often they have no oocytes, which means that, without treatment, these girls will not go through all the changes associated with puberty such as a growth spurt, breast development or menstruation.

Sometimes an ultrasound during pregnancy may already detect abnormalities such as a thickened nuchal fold. If this is the case, we typically schedule an amniocentesis.

Although intellectual development is usually normal, there is a higher risk of psychosocial and developmental problems (learning difficulties, limited motor skills, etc.).

If the NIPT detects a higher risk, the Centre for Medical Genetics at UZ Brussel will provide further guidance.

KLINEFELTER SYNDROME

Boys/men with Klinefelter syndrome are born with an extra copy of the X chromosome, also known as 'XXY'. They have a higher risk of:

- Being taller than their peers.
- Fertility problems: they are often infertile due to changes in the testes (testicle) that produce the male hormone (testosterone) and sperm.
- Delayed puberty or delayed sexual development.

Klinefelter syndrome is not usually associated with ultrasound abnormalities.

Mental development is usually normal, but there is a higher risk of developmental disorders (such as delayed language development and/or learning difficulties) and psychosocial problems.

If the NIPT detects a higher risk, the Centre for Medical Genetics at UZ Brussel will provide further guidance (Klinefelter Clinic: www.uzbrussel.be/klinefelterkliniek).

5. RESULTS

The result of the NIPT is usually available 4 working days after receipt of the blood sample. You can find the result on the UZ Brussel's patient portal (https://my.uzbrussel.be). Your healthcare provider will contact you in the event of an abnormal or inconclusive result.

Several results are possible:

5.1 LOW RISK

No indication of trisomy 13, 18 or 21 was detected. A normal result does not absolutely rule out another chromosomal anomaly, but NIPT is very reliable for detecting trisomy 13, 18 and 21.

5.2 HIGH RISK FOR TRISOMY 13, 18 AND 21

The Centre for Medical Genetics will schedule an appointment with you to discuss this result. An abnormal NIPT result does not provide absolute (100%) certainty, but there is a higher risk. In that case, we recommend invasive testing, preferably amniocentesis. Amniocentesis analyses the DNA of the foetus, rather than the DNA of the placenta. If you are considering termination of pregnancy, you must undergo this diagnostic test.

5.3 INCREASED RISK OF OTHER CHROMOSOMAL ABNORMALITIES

The Centre for Medical Genetics will schedule an appointment with you to discuss this result. In about 1 in 500 pregnancies, NIPT detects a trisomy of a chromosome other than 13, 18 or 21. In most cases, this trisomy is unlikely to be present in the foetus and is confined to the placenta. This is called confined placental mosaicism. Amniocentesis is done to confirm this. For certain chromosomes, this increases the risk of placental abnormalities. This can lead to foetal growth restriction, premature birth and/or preeclampsia.

5.4 INCREASED RISK FOR TURNER SYNDROME OR KLINEFELTER SYNDROME

The Centre for Medical Genetics will schedule an appointment with you to discuss this result. The accuracy of NIPT for these sex chromosome disorders is not yet known, but their detection is less reliable (and currently under investigation) than for Down's syndrome (trisomy 21). Moreover, there are several factors that complicate detection, such as a low amount of cfDNA (foetal fraction) or a twin pregnancy and/or vanishing twin (the death (disappearance) of one of a set of twins, see also 5.8).

5.5 ABERRATIONS IN THE MOTHER'S DNA

During the NIPT, we also analyse the mother's cfDNA. This allows us to also identify any anomalies in her DNA. If this is important for the mother and/or foetus, you will get the results of this screening. Amniocentesis may be necessary to check whether the foetus is also a carrier of this chromosome aberration.

In very exceptional cases, NIPT detects cancer in the mother. This is because cancer cells also release cfDNA into the mother's bloodstream. If the cancer cells have large chromosomal aberrations, these are visible in the NIPT pattern. We report these findings to enable faster cancer follow-up and diagnosis. Please note that NIPT cannot detect all cancers.

5.6 THE NIPT IS INCONCLUSIVE OR FAILED

In 3 to 5% of tests, NIPT fails to deliver a result. This is usually due to an insufficient amount of DNA (foetal fraction) or poor sample quality. In that case, we recommend doing the bloodwork again after 2 to 3 weeks, for free. We can usually deliver a conclusive result after a second analysis. Generally, we do not perform NIPT a third time.

5.7 FALSE POSITIVES AND FALSE NEGATIVES

FALSE POSITIVE

A false-positive test result means the NIPT indicates an abnormal result, which is not backed up by amniocentesis. This can happen if:

- confined placental mosaicism occurs: a chromosomal aberration is present in the placenta but not in the foetus. Usually the placenta and the foetus have the same chromosomal makeup. In very rare cases, however, this is not the case and this may result in a false positive result. In rare cases, confined placental mosaicism may cause preterm birth or foetal growth restriction.
- the mother is a carrier of a chromosomal anomaly and this is mistakenly thought to be a chromosomal aberration of the foetus.
- one of a set of twins has a genetic disorder and dies (vanishing twin, see 5.8). It then may seem as if the surviving foetus has this aberration.

Amniocentesis will indicate whether this is a false-positive result (the foetus is then found not to have the genetic disorder). In some cases, we recommend examining the placenta after birth for the aberration found. This examination is free.

FALSE NEGATIVE

A false-negative result means the result of the NIPT was normal although the foetus has a chromosomal aberration. This can happen if:

- There is too little foetal cfDNA in the mother's blood (foetal fraction).
- The composition of the cfDNA of the placenta does not match that of the foetus (confined placental mosaicism).

A false-negative result is detected if, for example, an ultrasound finds there are foetal abnormalities later in pregnancy. Amniocentesis, or a genetic test after birth, may indicate that there is a chromosomal aberration nonetheless.

5.8 TWIN PREGNANCIES

We can perform NIPT in identical and fraternal twin pregnancy. NIPT is not possible in a multiple pregnancy.

IDENTICAL TWINS

Identical twins usually share the same genomes. The NIPT result thus likely applies to both foetuses.

FRATERNAL TWINS

In the case of fraternal twins, with both twins being the same sex, we cannot determine whether sufficient DNA is present from both babies. It is possible that there may be more DNA of one foetus in the mother's blood. A recent large-scale study at Belgian genetic centres, however, revealed that the odds of missing an anomaly in fraternal twins are no higher than for identical twin or singleton pregnancies. We can therefore reliably perform NIPT even in fraternal twins.

VANISHING TWIN

A vanishing twin is a condition in which one of a set of twins or multiples dies early in the pregnancy. For weeks or even months afterwards, DNA of this foetus may remain present in the mother's blood. This also means that if NIPT detects a chromosomal aberration, we cannot determine whether it was caused by the vanishing twin or the surviving member(s) of the set of twins or multiples. We recommend performing amniocentesis in that case.

SCREENING FOR SEX CHROMOSOME ANOMALIES IN TWINS

NIPT usually cannot detect sex chromosome anomalies in twins.

6. INFORMED CONSENT

Before we perform NIPT, we need your consent. You give this on the application form on which you indicate which results you want to receive.
We try to inform you as much as possible with this brochure, but if you want more details, you can always make an appointment at the Centre for Medical Genetics of UZ Brussel.

7. PRACTICAL INFORMATION

Since 1 July 2017, the Belgian National Institute for Health and Disability Insurance (RIZIV/INAMI) reimburses NIPT from the 12th week of gestation. If you have Belgian health insurance, you only pay the co-payment as a patient. If you are a foreign patient, you can also make an appointment for NIPT, but you pay the full cost of the test and consultation yourself.

CONTACT DETAILS

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