

Non invasive prenatal test (NIPT)

Information leaflet

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Universitair Ziekenhuis Brussel



Centrum voor
Medische Genetica



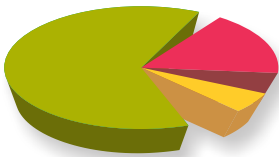
WHAT IS DOWN SYNDROME?

Though most babies are healthy, every baby has a small chance of having a physical and/or intellectual disability. In some cases, this disability can be due to an anomaly in the chromosomes, which are the carriers of our genetic material. Most people have 46 chromosomes, 2 of which determine the gender: XX for a female, XY for a male. Normally, every chromosomal pair consists of 1 maternal and 1 paternal chromosome. A baby with trisomy 21 (also known as Down syndrome) has three copies of chromosome 21 instead of two. This means that people with trisomy 21 have 47 chromosomes instead of 46.

Trisomy 21 is the most frequent chromosomal anomaly. Intellectual disability is the most important feature of trisomy 21. A minority of babies with Down syndrome have a congenital heart defect or another structural (physical) abnormality that can be detected via ultrasound. Other less frequent trisomies exist, trisomy 18 (Edwards syndrome) and trisomy 13 (Patau syndrome). The risk of Down Edwards or Patau syndrome becomes higher with increasing maternal age (from age 35, there is a marked risk increase).



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RISK CALCULATION

For those who wish to know, the risk of having a child with Down, Edwards or Patau syndrome can be estimated. Currently, the combination test and the NIPT (Non-Invasive Prenatal Test) are available for risk estimation. During the first pregnancy consultation, these different tests will be described to you in more detail. A first trimester ultrasound, with measurement of the neck fold and an overall check-up (as comprehensive and meticulous as possible) of your baby, is performed for every pregnancy. In other words, the ultrasound is also performed if you choose not to have the risk for Down syndrome calculated.

THE FIRST TRIMESTER COMBINED TEST

WHAT DOES THE FIRST TRIMESTER COMBINED TEST CONSIST OF?

The first trimester combined test calculates the risk of being pregnant with a baby with Down, Edwards or Patau syndrome by combining 3 factors: your age, the levels of 2 hormones in your blood (PAPP-A and free β -hCG) and 3 features examined upon your baby's ultrasound (neck fold, nasal bone and heart valve). This combined test is the most commonly used screening method for risk estimation.



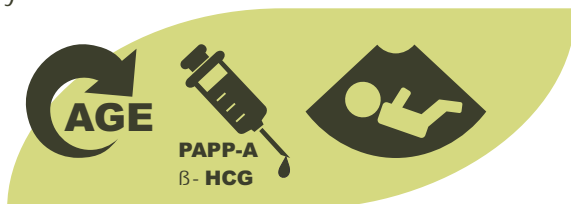
The blood sample for measurement of hormone levels is taken between 9 and 14 weeks of pregnancy, preferably before 11 weeks; it takes a few days to get all the results. The measurement of the neck fold takes place during the first trimester ultrasound, between approximately 11 and 13 weeks of pregnancy. Using an ultrasound, the amount of fluid beneath the skin around the baby's neck is measured as accurately as possible. Babies with Down, Edwards or Patau syndrome (but also other hereditary and non-hereditary conditions) tend to have an increased amount of fluid around the neck. Thus, the neck fold thickness is not only an indicator of Down, Edwards or Patau syndrome, but of several other conditions as well.

Furthermore, the calcification of the nasal bone is evaluated, as well as the heart valves' functioning. Babies with trisomy 21 have a slower calcification of the nasal bone and more frequently have a leak at the level of the heart valve. Babies with trisomy 18 or 13 have several malformations i.e. heart malformations, anomalies of the face or the limbs.

The combination of maternal age, blood hormone levels and sonographic features amount to a certain risk. An increased risk is a risk equal to or greater than $1/300$ (e.g. $1/110$).

The first trimester combined test has a sensitivity of approximately 80-85%, which means that 80-85 out of 100 babies with trisomy 21 will be detected with this test, while 15-20 will be missed.

For about 5% the combined test will lead to a false positive result. This means that when 100 women take the test, 5 of them will be told there is an increased risk of trisomy 21, even though their baby does not have trisomy 21.





WHAT ARE THE RISKS FOR MY BABY IF I CHOOSE THE COMBINED TEST?

The combined test is a non-invasive screening method. The blood sampling and ultrasound do not hold any risk for your pregnancy. Because the combined test leads to a false positive result in 5% of all cases, an invasive test will be recommended to 1 in 20 women because of an increased risk of trisomy 21, even though their baby does not have trisomy 21.



WHEN WILL I KNOW THE RESULTS OF THE COMBINED TEST?

If a blood sample was taken in advance, the sonographer (person performing the ultrasound) can calculate the risk immediately during the ultrasound and inform the mother of this risk. If the blood sample is taken on the day of the ultrasound, you will be contacted by your own obstetrician/gynaecologist or by the sonographer or midwife within one week, if the result is abnormal.



HOW MUCH DOES THE COMBINED TEST COST?

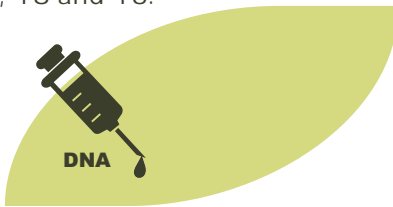
The combined test is reimbursed by your health insurance. This implies that you pay the same amount as for a standard pregnancy ultrasound. The blood tests will cost about 25 euro, if you do not have health insurance in Belgium.

NIPT

WHAT DOES THE NIPT CONSIST OF?

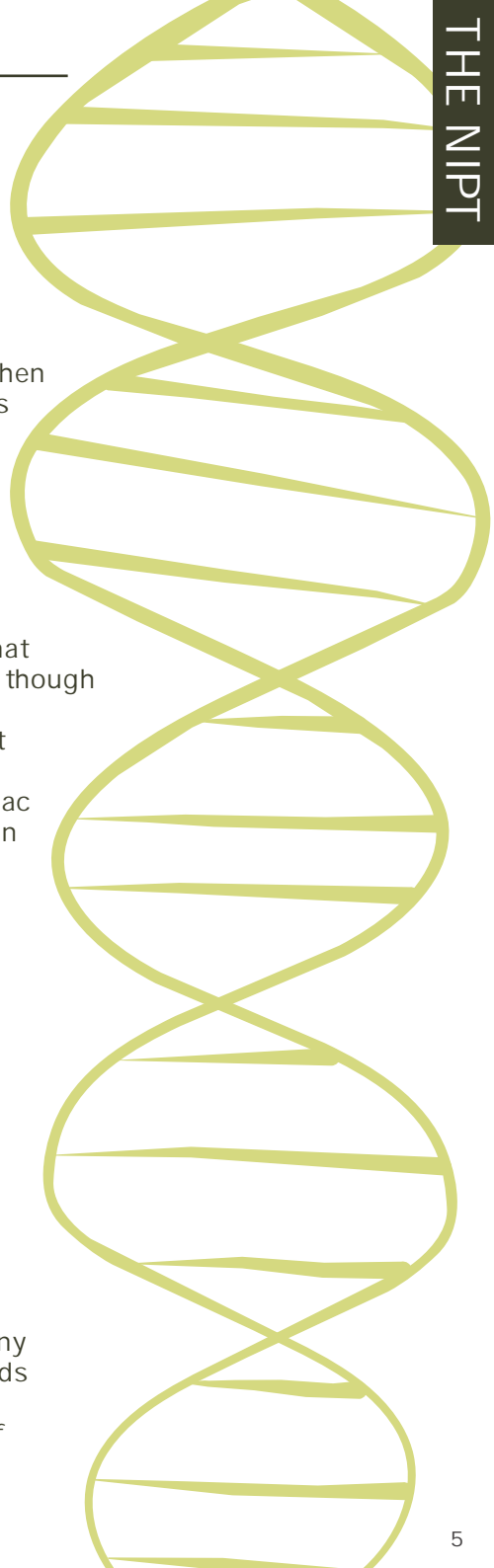
During pregnancy, fragments of the baby's DNA circulate in the mother's blood stream. By measuring the number of these DNA fragments, the number of chromosome 21, 18 and 13 copies can be determined. Thus, trisomy 21, 18 or 13 can be detected in the baby. The blood sample for this test can be performed at 11 weeks at the earliest. From then on, there is a sufficient amount of your baby's DNA circulating in your blood.

The NIPT has a sensitivity of more than 99%, which means that more than 99 out of 100 babies with trisomy 21, 18 and 13 will be detected by this test, while 1 or fewer will be missed. For 1% the NIPT will lead to a false positive result. This means that when 100 women take the test, 1 of them will be told that there is an increased risk of trisomy 21, even though her baby does not have trisomy 21. NIPT was developed in our laboratories with the utmost attention to quality (as for all other genetic analyses) and obtained accreditation from Belac (Belgian Accreditation institution) for detection of trisomy 21, 18 and 13.



WHAT ARE THE RISKS FOR MY BABY IF I CHOOSE THE NIPT?

The NIPT is also a non-invasive screening method. The blood sampling does not hold any risk for your pregnancy. Because the NIPT leads to a false positive result in 1% of all cases, an invasive test will be recommended to 1 out of 100 women because of an increased risk of trisomy 21, even though their baby does not have trisomy 21.





WHEN AM I ELIGIBLE FOR THE NIPT?

There are several situations in which you may consider the NIPT:

- You have had the first trimester combined test performed, showing an increased risk of trisomy 21, 18 or 13 ($> 1/300$)
- You have had a previous pregnancy with trisomy 21, 18 or 13
- You are 40 years or older and therefore have a strongly increased risk of having a baby with trisomy 21, 18 or 13 because of your age
- You are very worried and would like as much certainty as possible on trisomy 21, 18 or 13 without having an invasive test
- You don't have an increased risk, but want to minimize the residual risk for trisomy 21, 18 or 13 and avoid the risk of miscarriage related to an invasive test
- You have other reasons than the aforementioned for considering the NIPT. These reasons should be discussed with your doctor because certain genetic conditions require different tests



WHEN AM I NOT ELIGIBLE FOR THE NIPT?

NIPT is NOT possible in case of:

- A multiple pregnancy, except for twin pregnancy
- Previous blood transfusion, transplantation, stem cell, immuno or heparin therapy in the mother within the last 3 months
- Anomalies in the genetic material of the mother or father

In these cases, the first trimester combined test is preferable.

An invasive test is preferable in case of:

- Sonographic abnormalities in the baby (including neck fold measurement of $> 3.5\text{mm}$)
- (Severely) overweight mothers



WHAT ARE THE LIMITATIONS OF THE NIPT?

The NIPT determines the number of copies of chromosomes 21, 18, 13 and can detect the gender of your baby. The following conditions will therefore not be detected by the NIPT:

- Mosaicism of chromosome 21, 18 or 13
- Small abnormalities (deletions or duplications) of chromosome 21, 18 or 13
- Molecular monogenic abnormalities (e.g. cystic fibrosis or fragile X syndrome)

WHAT ARE POSSIBLE OUTCOMES OF THE NIPT?

1. The NIPT shows a **LOW** risk. This means that no indication for the presence of an extra copy of chromosome 21, 18 or 13 was found. Because the NIPT is a screening method (and therefore not a diagnostic test), a normal result cannot exclude trisomy 21, 18 or 13 with 100% certainty. Of 100 babies with trisomy 21, the NIPT will detect at least 99, while it will miss 1 at most.
2. The NIPT shows a **HIGH** risk. Although this is strongly indicative of trisomy 21, it does not incontrovertibly (with absolute certainty) mean that the baby has trisomy 21, 18 or 13. When the NIPT shows an abnormal number of copies of chromosome 21, 18 or 13, this result needs to be confirmed using an invasive test (CVS or amniocentesis). An invasive test allows for the direct examining of the baby's genetic material. Only after having this additional diagnostic test performed, will you know with complete certainty whether or not your baby has trisomy 21, 18 or 13.
3. The NIPT is **INCONCLUSIVE** or **FAILS** to provide a result. Because the NIPT is based on a risk estimation, there is a possibility that the statistical risk calculations will not be conclusive. In this case, the test cannot determine your personal risk of having a baby with trisomy 21. This may occur if, for example, the blood sample is taken before 11 weeks of pregnancy (when the amount of foetal DNA circulating in the mother's blood stream is not yet sufficient for a reliable NIPT), but also in overweight mothers. An inconclusive result or no result at all occurs in 3-5% of all samples taken. In this case, one can choose to have a new blood sample taken for the NIPT, or to have the first trimester combined test performed. In case of failure because of technical reasons, the NIPT will be repeated on a new blood sample without extra cost.
4. In rare cases, the NIPT may also detect other chromosomal abnormalities, such as partial trisomy 21, 18 or 13 in the baby but also clinically relevant chromosomal abnormalities in the mother. In these cases, the Centre for Medical Genetics will inform you and/or your obstetrician /gynaecologist.



WHEN WILL I KNOW THE RESULT OF THE NIPT?

The results are usually known after 2 weeks (exceptionally after 3 weeks), counting from the day of receipt of the blood sample.



HOW MUCH DOES THE NIPT COST?

This test is currently not reimbursed by your health insurance (RIZIV/INAMI), which brings the personal cost to 290 euro (+ yearly index). Please ask your health insurance(s) if partial reimbursement is possible.



WHAT IS THE DIFFERENCE BETWEEN THE COMBINATION TEST AND THE NIPT?

The difference between the combination test and the NIPT is that the NIPT detects more babies with trisomy 21 (99/100 with the NIPT versus 80- 85/100 with the combination test). Moreover, the number of false positive results is lower with the NIPT than with the combination test (1/100 with the NIPT versus 1/20 with the combination test). Thus, the NIPT allows for the detection of more babies with trisomy 21 and reduces the number of invasive tests (which have a risk of miscarriage). However, currently the NIPT is not (yet) reimbursed. Sometimes the NIPT is not possible or in 3 to 5% of cases, gives no conclusive NIPT result is obtained. In those cases and if anomalies are detected in the baby (including a neck fold measuring more than 3.5mm), an invasive test is always preferable.

AM I OBLIGATED TO HAVE THE RISK OF TRISOMY 21, 18 AND 13 CALCULATED?

The tests are offered to you *freely* (in a non-committal, open-ended way). Whether or not you choose to have a test performed, is entirely up to you; it is your own free choice.

Before you decide to have a test performed, it is advisable to reflect upon the following things:

- The combination test and triple test offer a risk estimation and do not offer absolute certainty on trisomy 21, 18 and 13.
- If the risk is elevated, an amniocentesis (or CVS), which implies a risk of miscarriage of 1/200, is the next step.
- What would I decide with regards to my pregnancy if I knew my baby had trisomy 21, 18 and 13?

Taking these things into consideration, you (along with your partner) can make the decision that is right for your specific situation.



ANY FURTHER QUESTIONS?

If you have any further questions after reading this information, you can contact your obstetrician/gynaecologist or the centre for medical genetics of your choice.

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