Answers to questions about the Non-Invasive Prenatal Test (NIPT)

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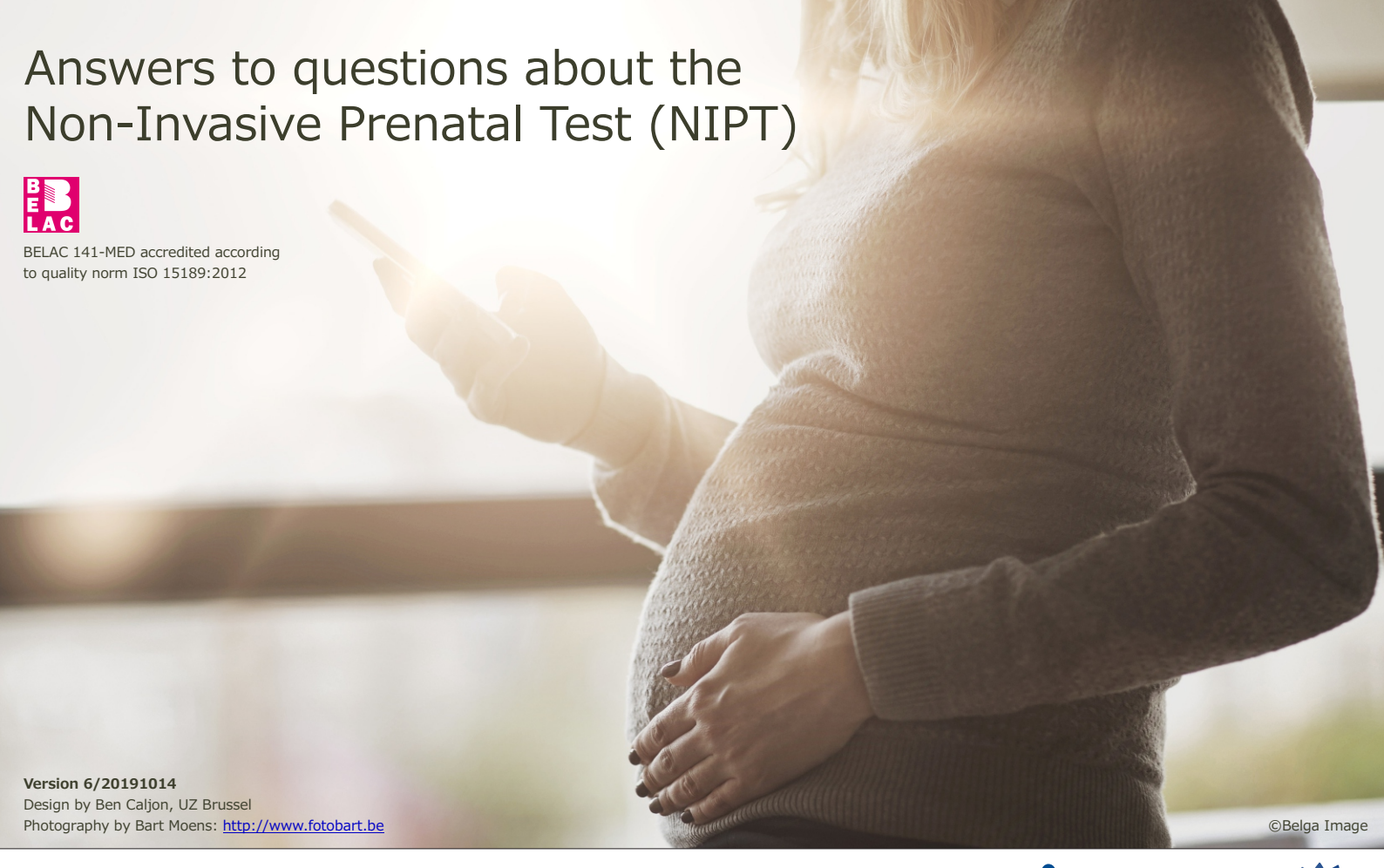

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Universitair Ziekenhuis Brussel

Centrum voor Medische Genetica

Hôpital Erasme

ULB

ULB Center of Human Genetics

BRIGHT

During pregnancy the risk of having a child with Down, Edwards or Patau syndrome can be estimated.

WHAT IS DOWN, EDWARDS AND PATAU SYNDROME?

Most babies are healthy, but 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 3 copies of chromosome 21 instead of the usual 2 copies. This means that people with trisomy 21 have 47 chromosomes instead of 46. Trisomy 21 is the most frequent chromosomal anomaly. Trisomy 21 causes intellectual disability, but physical features may be present as well.

Besides trisomy 21, other less frequent trisomies (three copies) exist like trisomy 18 (Edwards syndrome) and trisomy 13 (Patau syndrome).

WHAT IS YOUR RISK FOR DOWN, EDWARDS AND PATAU SYNDROME?

During pregnancy the risk of having a child with Down, Edwards or Patau syndrome can be estimated.

If you choose to have a risk estimation, a Non-Invasive Prenatal Test or NIPT, can be performed. This test is reimbursed by the Belgian health insurance. During the first pregnancy consultation, the NIPT will be described to you in more detail.

Keep in mind that ultrasound during the first trimester of pregnancy may also lead to a suspicion of a genetic or non-genetic condition in your baby. The NIPT analysis is complementary to, but certainly does not replace, first trimester ultrasound.

ARE YOU OBLIGATED TO HAVE THE RISK OF DOWN, EDWARDS OR PATAU SYNDROME ESTIMATED?

Absolutely not. Whether or not you choose to have a test performed, is entirely up to you; it is your own choice.

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

- The NIPT does not offer absolute certainty on the presence or absence of Down, Edwards or Patau syndrome. It remains a risk estimation. (See paragraph: What is the reliability of the NIPT?)

  If a high risk result is obtained, amniocentesis is recommended (this implies a small risk of miscarriage, of approximately 1/200). It is highly likely that the chromosomal aberration will be confirmed.
- What would you decide with regard to your pregnancy if you knew your baby had Down, Edwards or Patau syndrome or another severe genetic condition?

Taking these things into consideration, you (along with your partner) can make the decision whether or not to perform a test.

FIRST TRIMESTER ULTRASOUND MUST BE PERFORMED BEFORE THE NIPT

A first trimester ultrasound is performed in every pregnancy. During the ultrasound an overall check-up of your baby is performed. This may lead to a suspicion of a genetic or non-genetic condition in your baby. Keep in mind that sonographic abnormalities in the baby do not necessarily mean that the baby will be affected by a genetic condition. If sonographic abnormalities are observed, genetic counseling and pregnancy specific follow-up is recommended. In this case other diagnostic techniques, instead of or in combination with the NIPT, may be preferred. It is therefore strongly recommended to perform a first trimester ultrasound before the NIPT.

WHAT SONOGRAPHIC SIGNS MAY BE INDICATIVE OF AN ABNORMALITY?

Among others:

- Nuchal translucency: the nuchal fold thickness, the translucent area under the skin at the back of the baby's neck is measured precisely. Babies with Down, Edwards or Patau syndrome tend to have an increased amount of fluid around the nape of the neck. An increased nuchal translucency may also be present in other genetic or non-genetic conditions, like heart and/or skeletal defects.
- Characteristics of the nasal bone: development may be less in babies with trisomy 21.
- Functioning of the heart valve: babies with trisomy 21 more frequently have leakage at one of the heart valves.
- Other signs: babies with for example trisomy 18 or 13 may have several other malformations as well i.e. anomalies of the heart, face or limbs.

WHAT DOES THE NIPT CONSIST OF?

During pregnancy, fragments of the baby's DNA circulate in the mother's blood stream. These DNA fragments are derived from the different chromosomes. By measuring the number of these DNA fragments, the number of copies of chromosome 21, 18 and 13 can be determined, and so the presence of trisomy 21, 18 or 13 can be predicted. The blood sample for this test can be taken at 12 weeks gestation (since last menstrual period) at the earliest. Only then will there be a sufficient amount of DNA of the baby (in reality DNA of the placenta) circulating in the blood of the mother.

The 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) since January 2015.

WHAT CAN THE NIPT DETECT?

Today the NIPT is primarily used for the detection of Down syndrome, but trisomy 18 or 13, and the gender of the baby, can be detected as well. Furthermore, we also collect information concerning (parts of) other chromosomes, sometimes for example too many or too few copies of a chromosome, or smaller abnormalities called microdeletions or microduplications.

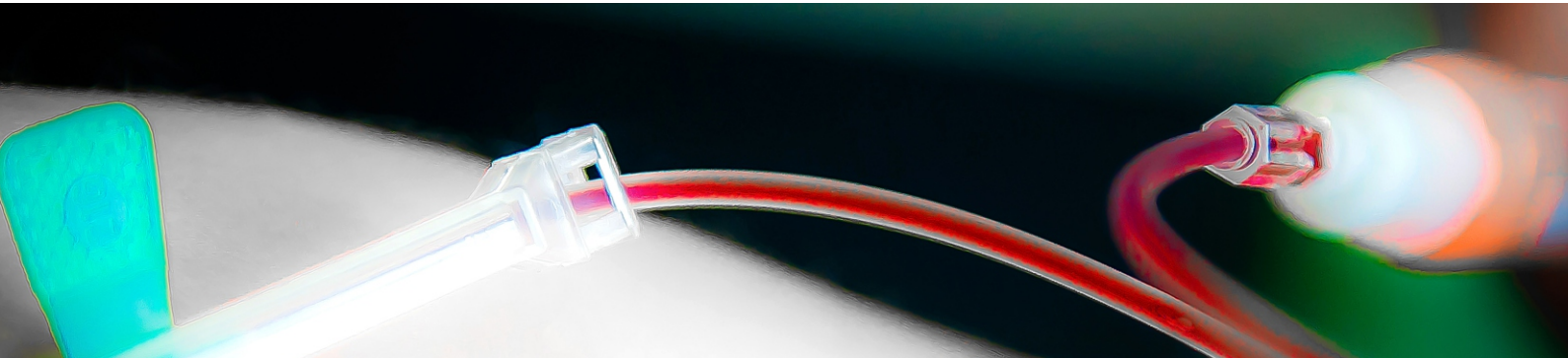
Considering that the blood of the mother is used to do the NIPT analysis, genetic abnormalities that are present in the mother may be detected as well. When these findings are of clinical relevance for your pregnancy, your baby or yourself, these findings will be communicated to you.

WHAT IS THE RELIABILITY OF THE NIPT?

- The NIPT is 99% reliable: more than 99 out of 100 babies with trisomy 21, 18 or 13 will be detected by this test, while maximum 1 will be missed.
- In approximately 0,2% of cases (or 1 in 500 women) the NIPT analysis will lead to a 'high risk' result for chromosome 21, 18 or 13 that cannot be confirmed in the baby or the mother. This is generally caused by the biological phenomenon known as 'placental mosaicism'. Placental mosaicism is when the abnormality is only present in the placental cells and is not present in the cells of the baby itself. These results will be followed up on in more detail and under professional guidance.

WHAT IS THE RISK FOR YOUR BABY IF YOU CHOOSE TO DO THE NIPT?

- The NIPT is a non-invasive screening method. Taking the blood sample does not hold any risk for your pregnancy or for yourself.



WHEN IS THE NIPT RECOMMENDED?

Since 1 July 2017, in Belgium, a NIPT analysis is reimbursed for **every** pregnancy (excluding a limited co-payment fee). Therefore you do not need a specific medical reason to perform the NIPT.

Nevertheless, the NIPT may be particularly recommended in the following situations:

- You are very worried and would like as much certainty as possible on your risk of having a baby with Down, Edwards or Patau syndrome without having an invasive test.
- You have had a baby with Down, Edwards or Patau syndrome in a previous pregnancy.
- You are 35 years or older and therefore have a strongly increased risk of having a baby with Down, Edwards or Patau syndrome.
- You have other reasons. These reasons should be discussed with your doctor because many genetic conditions require different tests.
- For patients without a Belgian health insurance: you have had a first trimester combined test performed which was indicative of an increased risk for trisomy 21 (>1/300).

WHEN ARE YOU NOT ELIGIBLE FOR THE NIPT?

The NIPT is **not possible** in case of:

- A multiple pregnancy (more than 2 foetuses).
- Recent (less than 3 months ago) blood transfusion, transplantation, stem cell or immunotherapy in the mother.

The NIPT is **more difficult** in mothers undergoing heparin therapy (a treatment to reduce the risk for accelerated blood clotting). You have a higher risk for an inconclusive NIPT result.
In these cases, the combination test is preferable.

An **invasive test (chorionic villus sampling or amniocentesis) is preferable** in case of:

- Sonographic abnormalities in the baby (including a nuchal translucency of >3.5mm).
- (Severely) overweight mothers (BMI>30), as the chance of a successful NIPT analysis is lower in mothers with a high BMI.
- Particular anomalies in your genetic material or that of the father of the baby.

WHAT ARE THE LIMITATIONS OF THE NIPT?

The following condition **will not be detected** by the NIPT:

- Molecular monogenic abnormalities e.g. cystic fibrosis (a genetic disorder affecting mainly the lungs) or fragile X syndrome (a genetic disorder causing intellectual disability), caused by a point mutation or a small error in a specific gene.

What **can generally not be detected** with certainty by the NIPT is:

- Mosaicism (if the anomaly is only present in part of the cells).
- Small abnormalities (microdeletions or -duplications, i.e. only a small part of a chromosome is missing or is additionally present).

WHAT ARE POSSIBLE OUTCOMES OF THE NIPT?

- **LOW RISK**: no indication for the presence of an extra copy of chromosome 21, 18 or 13 was found. Keep in mind that a normal NIPT result cannot exclude trisomy 21, 18 or 13 with 100% certainty because the NIPT is a screening method and not a diagnostic test.
- **HIGH RISK**: this is strongly indicative for a trisomy, but does not necessarily mean that the baby has trisomy 21, 18 or 13. A high risk NIPT result should be confirmed using an invasive test (amniocentesis). Via invasive testing the baby's genetic material is examined directly. Only then will you know with complete certainty whether or not your baby has trisomy 21, 18 or 13.
- **EQUAL RISK**: 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. An inconclusive result occurs in approximately 5% of all samples taken, mostly due to an insufficient fraction of fetal DNA in the blood of the mother. In this case, you can choose to have a new blood sample taken for a second NIPT, offered for free. In case of a second inconclusive NIPT result, this test will not be repeated again. As an alternative you can opt for a combination test (which should be performed before 14 weeks of pregnancy) or an amniocentesis. What the best option is for you can be discussed with your gynaecologist.
- **NO RESULT**: in case of failure because of technical reasons, the NIPT will be repeated on an additional blood sample without extra cost.
- **PRELIMINARY RESULT**: if additional analyses are performed in order to obtain a reliable risk estimation, your referring doctor will be notified via a preliminary result letter. These additional analyses do not require a new blood sample and usually the definitive NIPT result will follow within the week.

- **OTHER CHROMOSOMAL ABNORMALITIES**: in rare cases, the NIPT may also detect chromosomal abnormalities other than trisomy 21, 18 or 13, in the baby, or a clinically relevant abnormality in the mother (including suspicion of a cancer). In this case, the Centers for Medical Genetics (of UZ Brussel and/or ULB Erasme Hospital) will contact your referring doctor so that further monitoring of the pregnancy can be done, according to these findings.

WHEN WILL YOU KNOW THE NIPT RESULT?

We aim for a response time of 5 business days, starting from the day of receipt of the blood sample and signed NIPT request form.

HOW MUCH DOES THE NIPT COST?

As of the 1st of July 2017, the NIPT is reimbursed by your Belgian health insurance. Therefore, a maximum of 8,68 euro co-payment fee will be charged to the patient. If you do not have a health insurance in Belgium, the NIPT costs 260 euro (+ possible indexation).

SUMMARY REQUIREMENTS FOR NIPT

- First trimester ultrasound result

- Blood sample (not taken before 12 weeks gestation, counted from last menstrual period)

- Informed consent: https://www.uzbrussel.be/cmg/NIPTrequestform or scan this QR code

ANY FURTHER QUESTIONS?

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

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