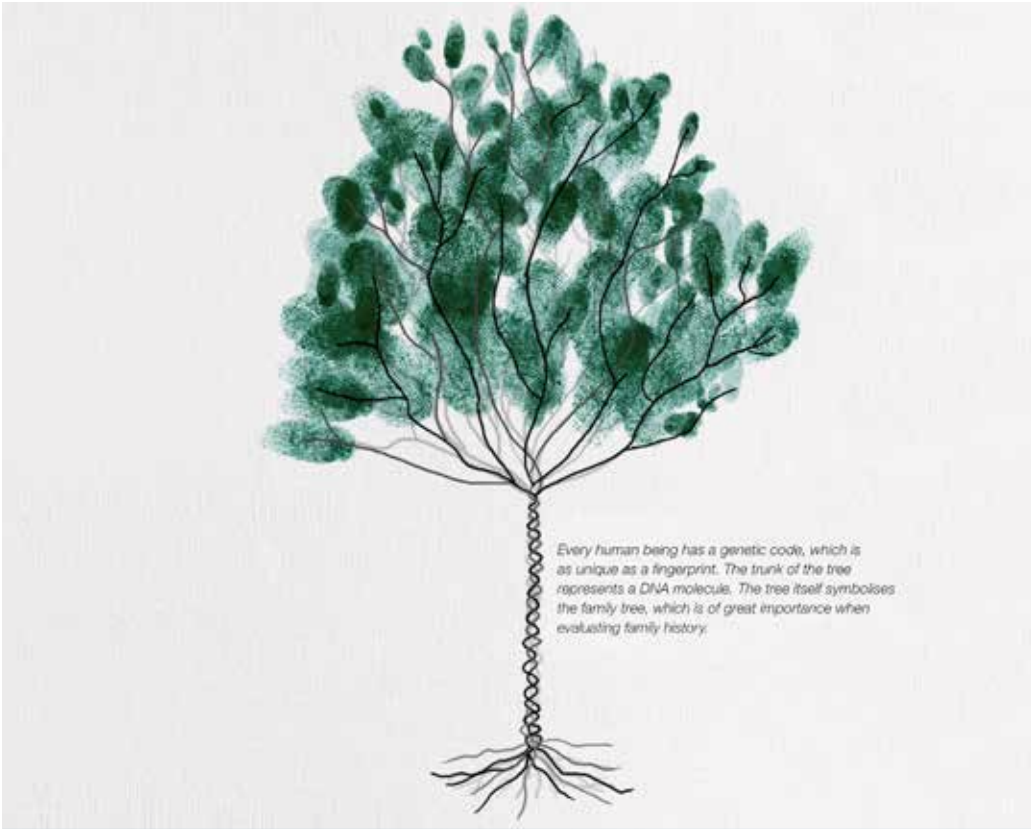


Every human being has a genetic code, which is as unique as a fingerprint. The trunk of the tree represents a DNA molecule. The tree itself symbolises the family tree, which is of great importance when evaluating family history.

PRE-IMPLANTATION GENETIC TESTING

PGT

UZ GENT

UNIVERSITEIT GENT

CONTENTS

01 WHAT IS A PRE-IMPLANTATION GENETIC TESTING (PGT)?

A pre-implantation genetic diagnosis or PGT is a specialised technique used to detect a genetic abnormality in an embryo. With the help of PGT, a known genetic disease or chromosomal abnormality in the child can be avoided. A PGT can also reduce the risk of miscarriage due to a chromosomal abnormality in the foetus (aneuploidy).

02 WHO FOR?

PGT is intended for would-be parents with an increased risk of having a child with a genetic disorder or for would-be parents with reduced fertility as a result of a chromosomal rearrangement.

In PGT, the genetic diagnosis is made on a few cells of the embryo that has developed in vitro. In this way, we can prevent a couple from becoming pregnant with a child who has inherited the genetic disease of which the parent(s) is/are a carrier.

When PGT is used because of a chromosomal rearrangement in one of the would-be parents, the chance of pregnancy is increased by selecting only the balanced embryos, the birth of a child with an unbalanced rearrangement can be prevented and/or repeated miscarriages can be avoided.

03 MEDICALLY ASSISTED FERTILISATION

A pre-implantation genetic test can only be performed in the case of a medically assisted fertilisation, and not in the case of a spontaneous pregnancy. The embryos are obtained by IVF (in vitro fertilisation) treatment, where one sperm cell is injected into one egg cell. This technique is called ICSI: intracytoplasmic sperm injection.

When an egg cell is fertilised with a sperm cell in the IVF laboratory, an embryo is created. Five to six days after fertilisation, some cells are removed from the embryo (embryo biopsy). The embryos are frozen for safekeeping. On the removed cells, we perform a genetic test to determine whether or not the genetic abnormality is present. Only the embryos that do not carry the tested abnormality are suitable for transfer into the uterus.

Process from ICSI to day 6 of the embryo

Day 0 **Day 1** **Day 2** **Day 3** **Day 4** **Day 5** **Day 6**

- **Day 0:** Insemination: one sperm cell is injected into one egg cell.
- **Day 1:** If the egg cell has been properly fertilised, two pronuclei are visible: one from the egg cell and one from the sperm cell.
- **Day 2:** The embryo develops and consists of 4 cells (cleavage stage).
- **Day 3:** The embryo consists of about six to eight cells.
- **Day 4:** The embryo grows and develops into a morula (16-32 cells).
- **Day 5:** The embryo develops into a blastocyst (>60 cells).
- **Day 5 to 6:** The embryo breaks through the protective capsule.

04 TYPE OF PGT

At the Centre for Medical Genetics, we carry out pre-implantation genetic tests for various indications.

PGT in monogenic disorders (comprehensive PGT-M, abbreviation coPGT-M)

These are genetic defects or mutations that are responsible for an autosomal dominant, autosomal recessive or X-linked disorder, or very occasionally a disorder with mitochondrial inheritance. With the coPGT-M technology, in addition to detecting the known genetic disorder, any additional chromosomal abnormalities in the embryo are also identified, e.g. trisomy 21 (which causes Down's syndrome).

Before the actual PGT, a specific test must be developed for each couple. In the genetics laboratory we investigate whether it is possible to accurately detect the familial mutation(s) on the cells of the embryo biopsy (2 to 8 cells). This test development takes approximately four months.
The following results are possible with coPGT-M:

For autosomal dominant disorders:

- Embryos without the genetic defect and without an additional chromosomal abnormality are suitable for transfer into the uterus.
- Embryos with the genetic defect and/or an additional chromosomal abnormality are not transferred into the uterus.

For autosomal recessive disorders:

- Embryos without mutation and without an additional chromosomal abnormality are suitable for transfer into the uterus.
- Embryos with one mutation (i.e. healthy carriers of the disorder) and without additional chromosomal abnormality are suitable for transfer into the uterus.
- Embryos with the two mutations (will develop the disorder) are not transferred into the uterus.
- Embryos with a chromosomal abnormality are not transferred into the uterus.

For X-linked disorders, of which women are carriers:

- Male embryos without the mutation and without an additional chromosomal abnormality are suitable for transfer into the uterus.
- Female embryos without the mutation and without an additional chromosomal abnormality are suitable for transfer into the uterus.
- Male embryos with the mutation (will develop the disorder) are not transferred into the uterus.

- Female embryos with the mutation are carriers of the disorder. For some X-linked disorders, female carriers may show signs of the disorder to a greater or lesser extent. If this is the case for the disorder in question, these embryos are not transferred into the uterus as stipulated by law.
- Embryos with a chromosomal abnormality are not transferred into the uterus.

For X-linked disorders, of which men are carriers:

- Male embryos (are not carriers of the mutation), which do not have an additional chromosomal abnormality are suitable for transfer into the uterus.
- Male embryos (are not carriers of the mutation), which do have an additional chromosomal abnormality, are not transferred into the uterus.
- Female embryos (are obligate carriers of the mutation) are not transferred into the uterus.

For mitochondrial disorders carried by women:

Only embryos with a mutation load of $\leq$ 15% are suitable for transfer into the uterus. However, any chromosomal abnormalities cannot be detected here since this type of PGT is performed using a different technology.

When the genetic defect of an X-linked recessive disorder is not known, but pedigree research or segregation analysis (family research) still shows that the woman is a carrier of the responsible genetic defect, PGT can be used to determine the gender of the embryos. In that case, only the female embryos are suitable for transfer into the uterus. They are unlikely to develop the condition.

In Belgium, it is not permitted by law to determine the sex of an embryo for any reason other than medical ones.

PGT for specific unbalanced structural chromosomal abnormalities (PGT-SR)

If one of the partners within a couple carries a balanced chromosomal abnormality, a prior development is usually not necessary. IVF treatment and the ICSI procedure can start almost immediately in the Department of Reproductive Medicine. Here, too, the PGT is performed on a few cells taken from the embryos around the fifth or sixth day after fertilisation.

PGT for aneuploidy screening (PGT-A)

This form of PGT can be used if we suspect that an embryo has an increased risk of chromosomal abnormalities. The partners themselves have a normal chromosome map. PGT-A is only offered in specific cases and after internal agreement. No prior development is required and IVF treatment at the Reproductive Medicine Department can start immediately. We follow the same procedure as for PGT-SR. Only the embryos that do not carry aneuploidy are suitable for transfer into the uterus.

05 DEVELOPMENT OF THE TEST

The development of the coPGT-M test takes about four months. We need blood samples from both would-be parents and possibly other family members to develop the test.

In the meantime, we schedule a first appointment at the Department of Reproductive Medicine. We will give you the date for this consultation after the consultation at the Medical Genetics Centre.

We ask the couple not to become pregnant spontaneously during the PGT development.

For PGT-SR and PGT-A, a prior development is not required and the IVF-ICSI procedure can be started immediately.

06 OTHER EXAMINATIONS IN THE GENETIC LABORATORY

Chromosome map

We draw up a chromosome map of both partners. In this process, chromosomes, the carriers of our genetic material, are put together in homologous pairs (one copy from the mother and one copy from the father) and ordered from large to small. The sex chromosomes are placed last. By creating the chromosome map, we can identify both abnormalities in the number of chromosomes (numerical abnormalities) and abnormalities in the size and shape of the chromosomes (structural abnormalities). If a chromosome map has already been made, it does not have to be done again.

Carrier testing

We also carry out a carrier test on both partners for two frequently occurring autosomal recessive disorders and one X-linked disorder: cystic fibrosis, spinal muscular atrophy (SMA), and fragile X syndrome (is only checked in the woman). In this way, we can greatly reduce the risk of having a child with these conditions.

Cystic fibrosis

Cystic fibrosis or mucoviscidosis is the most common serious autosomal recessive disease in people of the Caucasian race. About 1 in 25 people carry a mutation in the cystic fibrosis gene (CFTR gene). Cystic fibrosis is caused by a mutation in both copies of the CFTR gene. If both partners are carriers, the risk of an affected child is 25 per cent.

The most common symptoms of cystic fibrosis are tough mucus that is difficult to cough up, chronic respiratory infections and digestive problems. Cystic fibrosis cannot yet be cured. Today, the average life expectancy is 40 years.

Spinal muscular atrophy

Spinal muscular atrophy (SMA) is also a serious autosomal recessive disorder. One in 40 people is a carrier. SMA is caused by a mutation in both copies of the SMN1 gene. The disease affects the nerve cells in the spinal cord, causing the muscles to become poorly controlled and increasingly thin. This leads to progressive muscle weakness and/or paralysis. SMA cannot yet be cured.

Fragile X syndrome

Fragile X syndrome is the most common inherited form of intellectual disability in boys. The intellectual disability is always moderate to severe in boys.

The condition is less common in girls. About half of the girls with a mutation have learning difficulties or a mild to moderate intellectual disability. Women can be carriers of a so-called premutation. This means that they themselves do not have the syndrome, but they do have a risk of having a child with fragile X syndrome. About 1 in 250 women is a carrier of such a premutation.

These additional genetic examinations are carried out on the basis of a blood sample and take approximately six weeks. We deliver the results to the Department of Reproductive Medicine. In case of an abnormal result, we will inform you in writing or invite you for further genetic counselling.

Extended carrier screening or BeGECS

Couples are also free to take an extended genetic carrier screening or BeGECS (Belgian Genetic Extended Carrier Screening).
This test examines more than 1,000 genes linked to several serious hereditary diseases that are autosomal recessive or X-linked recessive. For each of the examined conditions, the most important mutations that are currently proven to cause the disease are checked. If these mutations are absent, the risk of being a carrier is smaller, but not completely excluded.

If, as a result of this test, there is an additional risk of having a child with a disorder, a test development for coPGT-M can also be carried out.

07 THE CONSULTATION

A physician-geneticist and a psychologist sit in at the PGT consultations wherever possible. The doctor provides all information on the medical-genetic component of PGT treatment. The psychologist can support you in your decision whether or not to choose PGT. The psychologist also listens to your experiences, e.g. the difficult road you have travelled so far to have a child and/or an unfulfilled desire to have children. Psychological support remains possible throughout the PGT process.

08 INFORMED CONSENT

At the end of the consultation in the Medical Genetics Centre, we will ask you to give your written consent to start the PGT treatment on the basis of the information you have been given. We then take blood samples from both partners.

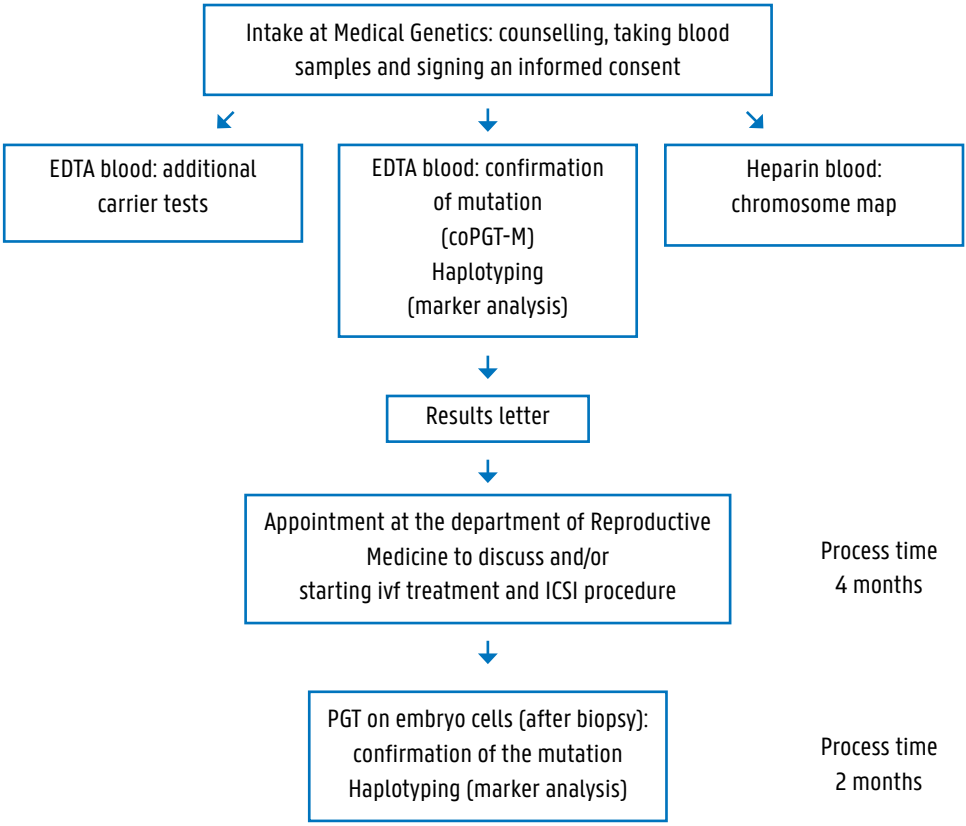
09 RELIABILITY OF PGT

PGT is a very reliable technique. However, we cannot give 100 per cent assurance. There is a (very small) chance of 1 per cent of a wrong diagnosis. This can mean that a healthy embryo is wrongly considered to be affected and therefore not suitable for transfer into the uterus. It can also mean that an embryo that does carry the abnormality is considered normal and is wrongly considered suitable for transfer into the uterus.

Therefore, we recommend having the result confirmed during pregnancy or after the birth of the child for 100 per cent certainty. During the pregnancy, this can be done with a chorionic villus sampling or amniocentesis, after birth with a blood test. If necessary, umbilical cord blood may be taken during childbirth. If you wait until after the birth, the PGT coordinator will contact you to schedule this blood sampling.

It is also possible that an embryo is not informative. This means that it is not clear whether the embryo is suitable for transfer into the uterus or not. In very exceptional cases it may be decided to transfer such an embryo after all. This is only done after consultation with the medical staff and the would-be parents. In such cases, we strongly recommend that a chorionic villus sampling or amniocentesis be carried out during pregnancy.

10 TREATMENT PROCESS STEP BY STEP



11 CHANCES OF PREGNANCY

The chance of pregnancy depends primarily on a number of individual factors such as the woman's age and the number of eggs obtained. In addition, the quality of the embryos and the number of embryos that do not carry the genetic diagnosis determine the success of the procedure. After transfer, an embryo must also implant in the uterus in order to result in a pregnancy. On average, the chance of becoming pregnant via PGT treatment is between 20 and 40 per cent per transfer.

12 PRICE

You can request a cost for the treatment from our PGT coordinator by sending an email to pgt.cmgg@uzgent.be. In Belgium, no reimbursement is provided by the health insurance fund for PGT-A. As mentioned earlier, couples can opt for an extensive carrier screening test without any obligation; this test, too, is not reimbursed by the health insurance fund.

For foreign couples, it is important to ask the health insurance company in advance for approval to reimburse the PGT treatment.

13 WHAT HAPPENS TO THE UNUSED EMBRYOS?

Embryos carrying the investigated abnormality and uninformative embryos may be destroyed or donated for further scientific research. Further explanations are available from the Reproductive Medicine Department.

14 APPOINTMENT

Make an appointment

You can make an appointment for a consultation at the Centre for Medical Genetics by sending an email to pgt.cmgg@uzgent.be. The PGT coordinator will deal with your question as quickly as possible. Be sure to provide the following information:

- surname and first name, date of birth, address and telephone number of both partners
- the disease for which you want a PGT
- a results letter, if you have one
- clarify whether it is a request for information or a request to initiate a PGT procedure

On the day of the consultation, you and your partner must register at the central reception and registration desk (entrances 50 or 12). Then come to the Medical Genetics Centre (entrance 81).

Cancelling an appointment

There is a great demand for PGT and there is a long waiting time. Therefore, we ask you to cancel the appointment in time if you are unable to come (at least 24 hours in advance).

If blood samples were taken for the test development and you decide not to proceed with the PGT treatment after all, please let us know as soon as possible by sending an email to pgt.cmgg@uzgent.be. If the test development has already started when you stop the procedure, you will still have to pay for the PGT setup and the carrier tests.

15 PGT TEAM

Sandra Janssens,
clinical geneticist

Virginie Szymczak,
PGT Coordinator

Sabine Hellemans,
psychologist

Ariane Van Tongerloo,
psychologist

Paul Coucke,
laboratory supervisor molecular lab - connective tissue lab

Sofie Symoens,
laboratory supervisor molecular lab - connective tissue lab

Björn Menten,
laboratory supervisor cytogenomics

Annelies Dheedene,
laboratory supervisor cytogenomics

Machteld Baetens,
supervisor cytogenomics

NOTES

NOTES

Centre for Medical Genetics

T +32 (0)9 332 36 03
info.cmgg@uzgent.be
www.uzgent.be/medischegenetica

Universitair Ziekenhuis Gent
C. Heymanslaan 10 | B 9000 Gent
T +32 (0)9 332 21 11 | **E** info@uzgent.be

www.uzgent.be
Volg ons op

vu.: Eric Mortier, gedelegeerd bestuurder UZ Gent, C. Heymanslaan 10, 9000 Gent – Mirto Print – 040051 – Oktober 2021 – versie 1