VARTA
Victorian Assisted Reproductive Treatment Authority

UNDERSTANDING THE GENETIC HEALTH OF EMBRYOS

Preimplantation genetic testing for aneuploidy

What is preimplantation genetic testing for aneuploidy?

Preimplantation genetic testing for aneuploidy (an abnormal number of chromosomes; PGT-A) is a testing technique that can help choose embryos that appear genetically normal for transfer. It is also known as preimplantation genetic screening (PGS).

Using embryos with the right number of chromosomes may increase the likelihood of successful implantation and reduce miscarriage following IVF for some women.

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The purpose of this document

VARTA provides independent information and support for individuals, couples, and health professionals on fertility, infertility, assisted reproductive treatment (ART) and the best interests of children born from ART.

This brochure is intended as a general introduction to this topic and should not be seen as a substitute for advice from doctors or other health professionals.

Information contained in this brochure was correct at the time of writing; however, as technology advances rapidly and new studies are conducted, it is important to check information with your fertility specialist.

Further information can be obtained from ART clinics and clinical genetics services.

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Common terms and their meanings

Advanced maternal age: When describing a woman's age with respect to her fertility, advanced maternal age refers to a woman aged 35 years or older.

Aneuploid: Abnormal number of chromosomes in a cell. In humans, an aneuploid cell has more or less than 46 chromosomes.

ART: Assisted reproductive technology. Technological and other methods to achieve pregnancy.

Blastocyst: A stage of embryo development that occurs five to six days after fertilisation, when cells arrange themselves into two areas – the inner cell mass and the trophectoderm.

Clinical pregnancy: A pregnancy confirmed by both high levels of the hormone hCG and visualisation of the embryonic sac by ultrasound.

Chromosome: The structures inside every cell into which genes are packaged. Each cell has two copies of each chromosome – one from each parent.

DNA: Deoxyribonucleic acid; molecule that contains the genetic code that determines the characteristics of the organism.

Euploid: The normal number of chromosomes in a cell. In humans, the euploid number is 46.

Embryo: The stages of development of a fertilised egg up to 11 weeks gestation.

Embryo biopsy: Collection of cells from the embryo in the laboratory.

False negative: When a test shows that an abnormality or condition is not present, when in fact it is.

False positive: When a test shows that an abnormality or condition is present, when in fact it is not. A type of 'false alarm'.

Gene: Section of DNA that contains the instructions (genetic code) to make molecules and proteins. Every person has two copies of each gene – one from each parent.

Genetically normal: Chromosomes have a normal number (euploid), and have no missing, added or switched portions of DNA.

hCG: Human chorionic gonadotropin; a hormone produced by cells in the placenta. Levels of hCG in urine and blood can be used to indicate a pregnancy.

Inner cell mass (ICM): The group of cells inside the blastocyst, which form the fetus.

IVF: In-vitro fertilisation. An assisted reproductive technology where an egg and sperm are combined in the laboratory before being transferred to the woman's uterus.

Karyotype: The number and physical appearance of the chromosomes in a cell. This test is performed to assist in determining if an individual has any changes in their chromosome structure.

Monosomy: One copy of a particular chromosome instead of two.

Mosaicism: A situation where some cells in an embryo have a different genetic structure (chromosome number or DNA arrangement) compared to other cells in the same embryo.

Ovarian reserve: Describes the capacity of the ovary to produce eggs.

Sex chromosomes: The chromosomes that determine sex – usually females have two X chromosomes while males have one X and one Y sex chromosome.

Trisomy: Three copies of a particular chromosome instead of two.

Trophectoderm: The outer layer of the blastocyst, which forms the placenta.

Zygote: The single cell formed by the combination of DNA from a sperm and an egg.

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Trying for a baby can be difficult, frustrating and completely overwhelming. Knowing what to expect and exploring your options can help make this process a little easier. Remember that information you receive can take a while to sink in. It is a good idea to discuss your options and concerns with your fertility specialist and supportive people, and seek further help if required.

Understanding the genetic makeup of embryos

Genetic testing is used to identify embryos with genetic abnormalities. To understand this process, it can help to understand a little about what makes an embryo appear genetically 'normal' or 'abnormal'.

Chromosomes: Each cell in the human body contains packages of genes called chromosomes. Normally, each cell has 46 chromosomes arranged in 23 chromosome pairs (half from each parent). Females have two X chromosomes, and males have one X and one Y chromosome. (See Figure 1.)

Sometimes cells have extra or fewer chromosomes. This is called aneuploidy. In most cases, embryos with chromosomal abnormalities are unable to progress to a healthy pregnancy and perish early. Pregnancies arising from aneuploid embryos can result in rare conditions like Down syndrome (Trisomy 21) (see Figure 2), Turner syndrome (45,X) and Klinefelter syndrome (45,XXY).

Sometimes cells have a structural abnormality in their chromosome. This is called a chromosomal rearrangement. These abnormalities can include 'translocations' (where parts of two chromosomes swap places) (see Figure 3) or 'inversions' (where a section of a chromosome is cut out, turned end to end, and reinserted back into the chromosome). People with a chromosomal rearrangement can experience infertility and miscarriage and, in some cases, have a child with a severe disability. Sometimes chromosome rearrangement in a parent causes embryos with the wrong amount of DNA. These embryos do not usually develop normally and so usually cannot become a healthy baby.

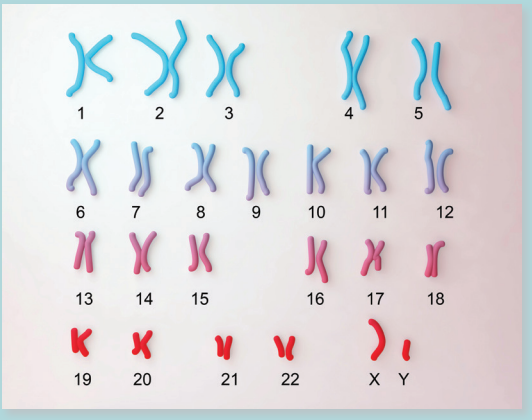

Figure 1 - Chromosomes in a male with 46 chromosomes

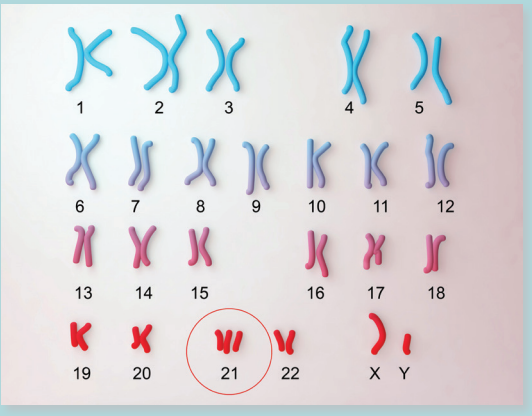

Figure 2 - Chromosomes in a male with Down syndrome (Trisomy 21)

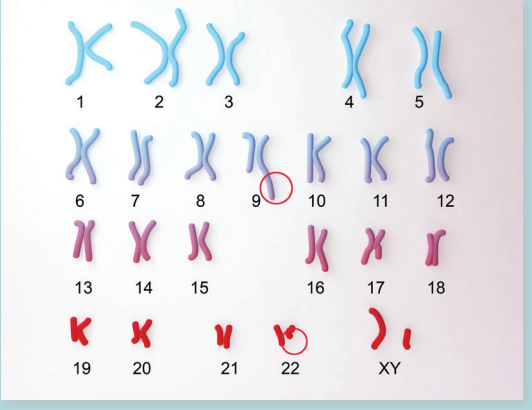

Figure 3 - Chromosomes in a male with a chromosomal rearrangement (translocation). In this example, parts of chromosomes 9 and 22 have switched places.

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Preimplantation genetic testing for aneuploidy

What is preimplantation genetic testing for aneuploidy (PGT-A)?

Pre-implantation genetic testing for aneuploidy
PGT-A is a scientific method used to assess whether an embryo has the correct number of chromosomes (called 'euploid') or has more or fewer chromosomes (called 'aneuploid').

In humans, there are 46 chromosomes in a normal cell. One reason that embryos fail to implant or miscarry is they have an abnormal number of chromosomes.

PGT-A allows clinicians to select an embryo with the correct number of chromosomes for transfer to a woman's uterus. By excluding aneuploid embryos, the chance of a successful embryo transfer can be increased in some women.

PGT-A cannot be used to alter or fix the number of chromosomes in an embryo.

Chromosome abnormalities in human embryos are common in women of all ages, but they occur more frequently in some women. This includes women who are older in their reproductive life, who have a history of recurrent pregnancy loss, who have had a previous aneuploid pregnancy or have had recurrent unsuccessful attempts at IVF.[1]

When is PGT-A performed?

PGT-A can be used to screen for an abnormal number of chromosomes (aneuploidy) in women who:

- have had several unexplained miscarriages
- have had previous failed IVF cycles
- have had a previous aneuploid pregnancy (e.g. Down syndrome)
- are of advanced maternal age (older than 35 years).

Advantages of PGT-A

Through selecting embryos that appear chromosomally normal:

- the chance of having a child with a condition caused by an abnormal number of chromosomes (aneuploidy) is decreased
- the likelihood of miscarriage is reduced
- the number of cycles required for a successful embryo transfer and pregnancy can be reduced in some women.

It is important to note that PGT-A does not guarantee a pregnancy, or the live birth of a child with no health or genetic conditions.

What does genetic testing of embryos involve?

PGT-A adds one extra step to the IVF process. This process usually has the following six steps.

1. **Assisted reproductive technology techniques are used to create embryos**

   An embryo is formed when a sperm and egg combine. PGT-A can only be performed with IVF procedures because cells must be collected (biopsied) from the embryo.

2. **Embryos are grown in the laboratory for five to six days**

   During this time, each embryo grows and develops. Embryos start as a single cell and keep dividing and growing to form a ball of cells. By five to six days after fertilisation, the embryo reaches the blastocyst stage. This is where the cells have organised themselves into two areas - the inner cell mass (which will become the fetus) and the trophectoderm (which will become the placenta).

3. **Cells are removed from the embryo for genetic testing**

   On days five to six, approximately five to eight cells are removed from the trophectoderm layer (which will become the placenta) and sent for genetic testing. Biopsy cannot be done if the embryo quality is poor or the embryo does not continue to develop normally.
   Your fertility specialist will discuss the timing and appropriateness of your biopsy with you.

4. **Genetic testing is performed on the cells that have been removed**

   The time to obtain results can range from days to several weeks, depending on the type of test performed. Embryos are usually frozen while waiting for PGT-A results.

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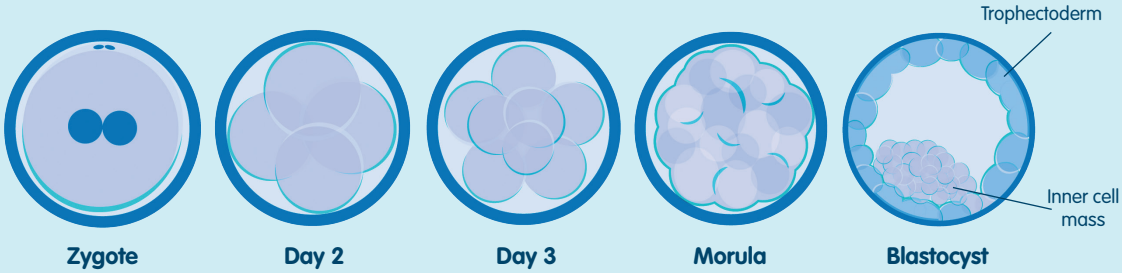
Initial stages of embryo development



5. **Embryos are sorted into those suitable for transfer and those that are not**

   Embryos that appear chromosomally normal will be used for transfer to the uterus or will be kept frozen for future transfer. Those embryos that do not appear chromosomally normal are discarded.

6. **Embryos are transferred to the woman's uterus**

   A frozen embryo can be warmed and transferred to the uterus during the period when a woman's body is receptive to implantation (around five days after ovulation). It is recommended that one embryo is transferred to the woman's uterus at a time.

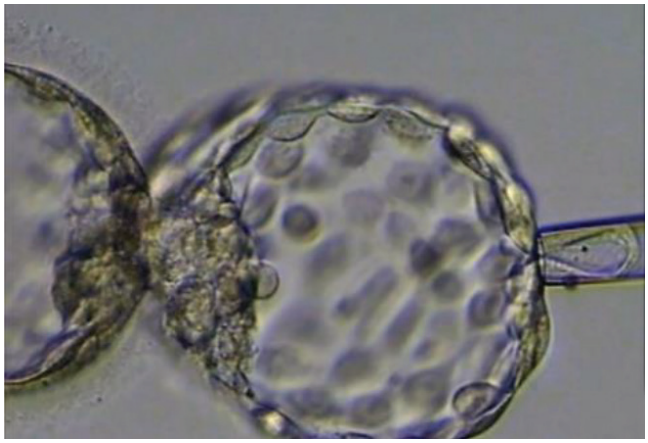


Figure 4 - A blastocyst biopsy. Cells are removed from the trophectoderm leaving the inner cell mass (left) intact.
Photo courtesy of Melbourne IVF.

When is PGT-A performed?

The chance of a successful pregnancy and healthy baby following IVF depends on many factors including age, reason for infertility, genetics, lifestyle (e.g. smoking, weight), and quality and number of embryos reaching the blastocyst stage. For more information on IVF success rates, see the VARTA website.

It is hard to determine if IVF with PGT-A improves success rates. This is because different studies use different methods, different aged women and different definitions of 'success'. For example, some studies define success as successful implantation of an embryo in the uterus, while others define it as a live birth per cycle or a live birth per transferred embryo.

In women who are predicted to have a high proportion of abnormal embryos (e.g. women over 37 years of age), PGT-A to select euploid embryos appears to decrease the chance of miscarriage, and increase the chance of live birth per embryo transfer.[2-5] However, it is important to remember that many women of advanced maternal age do not achieve an embryo suitable for biopsy.

Younger women in whom fewer embryos have spontaneous genetic abnormalities have not been shown to benefit from PGT-A.[4]

Like all ART treatments, genetic testing of embryos does not provide a guarantee of pregnancy or the live birth of a healthy baby. It also does not guarantee the health of any resulting child.

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Precautions when considering PGT-A

PGT-A is not a perfect tool. There are many reasons for this.

Not every cell in the embryo is genetically identical

It is possible that some cells in an embryo have one or more chromosome abnormalities, while the remaining cells are chromosomally normal. This is referred to as 'mosaicism'. This means there is a small risk the results may show the cells are abnormal when the rest of the embryo may be genetically normal (i.e. the test results may be a false positive).[6] This can lead to an embryo being discarded that may, if transferred, have led to the birth of a healthy baby. It is also means that an embryo considered to be 'normal' following PGT-A, may have chromosome abnormalities that were not able to be detected (i.e. the test result maybe a false negative).

There are technological limitations in the scientific methods used for PGT-A

The procedures used for genetic screening are improving, but there is always a risk of error. This is mainly due to the technical challenges of testing such small samples. Although the risk of error is very low (less than five per cent), there is a small chance that the test results will come back normal even where there is a genetic abnormality. Couples at risk are advised to confirm the results during pregnancy. These can be done by chorionic villus sampling (CVS) or amniocentesis, which are other genetic testing techniques performed on placental tissue or amniotic fluid during the first trimester of pregnancy. In some situations, PGT results can also be confirmed by testing fetal DNA in the mother's blood. It is also important to note that abnormalities that involve small parts of chromosomes will not be detected by PGT-A, and can only be detected by CVS or amniocentesis.

PGT-A may damage the embryo

A small number of embryos do not survive the biopsy required for PGT-A. However, most embryos do survive and continue to grow and develop normally. As genetic testing is a relatively new procedure, long-term effects of cell collection on child development are not yet known.

Embryos may not survive the thaw process

Embryos are frozen while waiting for PGT-A results. While most embryos selected for use experience no problems when thawing, there is a small chance some embryos may not survive the thaw process. These embryos are not able to be used for further treatment.

PGT-A may not be able to be performed

An embryo suitable for biopsy must be well developed, suitable for freezing and have protruding cells that can be biopsied ('hatching').

FAQs

Does genetic testing increase the chances that I will fall pregnant?

This is different for everyone. There are some groups that may benefit from having genetic testing performed, while for others there is no evidence to show it makes a difference. Genetic testing does not provide a guarantee you will fall pregnant, and does not guarantee the health or genetic makeup of a child.

Does PGT-A guarantee my child will be born live, healthy and genetically normal?

No. Unfortunately there are biological and technological limitations that limit how much information these techniques can provide. The chances of having a child with a genetic health condition are reduced, but not eliminated.

Does collecting cells for PGT-A damage the embryo?

There is a small degree of risk: approximately one in every 200 embryos does not survive this process. However, most embryos do survive and continue to grow and develop normally.

Does PGT-A affect the genes in the embryo?

No. Genetic testing is just a diagnostic procedure. It does not alter the genetic makeup of the embryo. It is important to understand that PGT-A does not fix fertility problems, nor does it fix the genetic errors that occur in embryos.

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How long before I get the results from my genetic test?

The time taken to get results will depend on the test performed. Test results generally take between one to three weeks to complete. Embryos will be frozen while waiting for your results.

If PGT-A results come back normal, does that mean my child will be healthy and genetically normal?

Unfortunately, there is still some risk that your child will have a health or genetic condition even if the PGT-A result comes back normal. It is important to note that aneuploidy, the type of genetic abnormality detected by PGT-A, is only one of many types of genetic problems that can affect a developing baby. Other types of genetic problems are not detected by PGT-A. In addition, there is a small chance that PGT-A will fail to detect an aneuploidy that is present in the embryo. You may choose to have further tests in pregnancy.

Does freezing between genetic testing and transfer affect the embryo?

There is no evidence to suggest that freezing affects the embryo. Frozen embryos that are warmed successfully are just as likely to result in a pregnancy as fresh embryos.

Does PGT-A increase the risk for the mother?

The risks to the mother are the same in IVF with and without PGT-A. It is a good idea to discuss the risks of IVF with your fertility clinician. For more information about these risks, see the publication *Possible health effects of IVF*, available on the VARTA website www.varta.org.au

Does it cost extra?

Yes. The costs of genetic screening can be expensive and are in addition to the costs of IVF. These costs will be provided by your clinic. These costs are not covered by Medicare.

Can I choose the sex of my baby?

No. Social sex selection is not allowed in Australia. This is only allowed when it is used to reduce the risk of a sex-specific genetic abnormality.

Questions to ask your fertility specialist

Is genetic testing necessary?

PGT-A is an optional procedure and is not required to proceed with the IVF process. In some situations, PGT-A can provide useful information to guide future decisions. Your fertility specialist will be able to help you with information about whether genetic testing is right for your situation.

Am I a good candidate for PGT-A?

PGT-A does not benefit everyone, as each situation is different. It is important to discuss with your fertility specialist whether PGT-A is right for you.

How many embryos do I have available for testing?

The number of embryos available for testing will depend on your own circumstances. Sometimes a couple may decide with their fertility specialist not to do PGT-A when there are a limited number of embryos that reach the blastocyst stage. Your fertility specialist can explain your options and advise whether genetic screening is right for you.

What happens if my embryos are tested and they all come back abnormal?

This depends on your individual circumstances. In most cases, this will mean that the embryos are not suitable for use. A possible exception is when an embryo carries a mosaic abnormality, that is, is made up of a mixture of chromosomally normal and abnormal cells. There are a few small studies that have reported healthy babies after transfer of embryos with some degree of mosaicism.[6-9] Your fertility specialist can discuss your results and your options with you.

Remember, there is no such thing as a bad question to ask your fertility specialist. They are there to help you.

IVF is a very personal experience and it is important you understand the procedure and your options. So, feel free to ask questions. This can help reduce some of the stress through this challenging time.

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