PGT-A (Pre-Implantation Genetic Screening) Patient Information

Summary of PGT-A

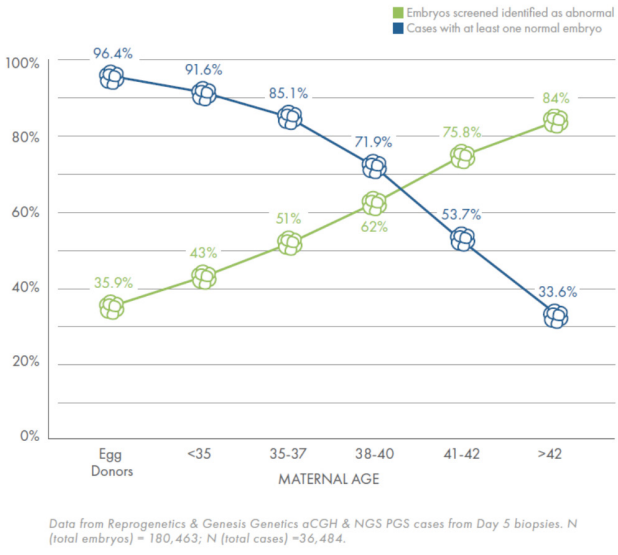
PGT-A (also known as Pre-implantation Genetic Screening (PGS)) is a method of screening embryos for chromosomal abnormalities prior to transfer back to the womb at the time of IVF. We know that chromosomally normal embryos are more likely to result in a successful pregnancy and livebirth. PGT-A is a selection tool to increase the likelihood of a healthy on-going pregnancy and is not a guarantee of pregnancy.

What are chromosomes?

Chromosomes are the packages that carry our genetic information. We normally have 46 chromosomes (23 pairs). The genetic information carried by the chromosomes is our body's instruction manual for how we grow, develop and function.

What happens if an embryo has an incorrect number of chromosomes?

It is expected that a proportion of all embryos formed will be chromosomally abnormal. These are known as aneuploid embryos. This is true whether the embryo was formed through natural conception or assisted conception (IVF / ICSI). The likelihood of an embryo carrying a chromosomal abnormality increases with age (Fig 1). Typically, in women who are 35-37 50% of embryos will be chromosomally abnormal, this figure rises to 75% in women in the 41-42 age group. This explains the lower pregnancy rates and increased miscarriage rates in women as they get older.



Data from Reprogenetics & Genesis Genetics aCGH & NGS PGS cases from Day 5 biopsies. N (total embryos) = 180,463; N (total cases) =36,484.

Fig 1 - Provided by Cooper Genomics

Some embryos may carry an extra copy of a chromosome whereas some embryos may be missing a chromosome, in some cases there is complete duplication of a full set of chromosomes. A chromosomally abnormal embryo is less likely to implant and more likely to result in a miscarriage. Chromosomally abnormal embryos rarely result in a livebirth and if they do there can be associated health problems for the child (e.g. Down's Syndrome).

In some cases, an embryo with the wrong number of chromosomes will spontaneously stop growing during its development in the laboratory and will not form a blastocyst (day 5/6 stage embryo). These embryos would not normally be considered for transfer. However, the majority of abnormal embryos will not stop growing until they have been transferred into the uterus. The major difficulty faced in the laboratory is that they are often indistinguishable from their normal counterparts judging by their appearance alone. There is a risk therefore that an aneuploid embryo would be recommended for transfer instead of a normal embryo, which may explain some unsuccessful IVF treatments.

Are an embryo's chromosomes routinely tested?

In most cases the answer is 'No'. In the IVF laboratory, the embryologist will look at the embryos down the microscope and grade them based on their physical appearance (morphology). The assumption is that the better the appearance, the better the quality of the embryo and hence it is more likely to implant. The only way of looking at the chromosome content of the embryo is by performing a biopsy of the cells and doing a PGT-A test.

Who is PGT-A suitable for?

Theoretically anyone undergoing IVF could have PGT-A, however it is more likely to benefit those couples that have a greater likelihood of having a chromosome problem in their embryos.

These are:

- Couples with a history of recurrent miscarriages
- Couples who have had several failed IVF attempts
- Couples who have had previous pregnancies affected by chromosome abnormalities
- Women over the age of 37

PGT-A may reduce these risks, although this has not been conclusively proven.
PGT-A cannot be used for sex selection purposes, which is illegal in the UK. It is only indicated for genetic/medical reasons. BCRM staff do not know the sex of the embryos when the results are received.

What is PGT-A?

PGT-A increases the likelihood of a chromosomally normal (euploid) embryo being transferred back at the time of IVF treatment.

Embryos are created using IVF / ICSI in the usual way. Once the embryos have reached the advanced (day 5 or 6) embryo stage (also known as the blastocyst stage), a small sample of cells are removed from the outside of the embryo, known as the trophoectoderm, using a microscopic laser. These cells are known as 'extra-embryonic' and produce tissues such as the placenta. There are over 100 trophectoderm cells in a blastocyst so the removal of very few of these cells rarely impacts on the embryo. The cells are sent for genetic analysis at a genetics laboratory and the chromosomes are assessed using a technique called Next Generation Sequencing (NGS). Meanwhile the blastocysts will be frozen, whilst the results of the genetic screening are awaited, this means that there will be no fresh embryo transfer in this cycle. The results take a minimum of 2-3 weeks to come back from the point of biopsy. Unfortunately, due to the time and expertise involved in biopsy it is not always possible to biopsy the blastocyst fresh. It may therefore be necessary to freeze the blastocyst and schedule thaw, biopsy and re-freeze on another day. Our embryology team will inform you at the time of egg collection when your embryo biopsy will most likely occur. Depending on the timing of the biopsy a consultation will be arranged for you with your fertility consultant to discuss the PGT-A results. If the results indicate that there is at least one embryo suitable for transfer, a Frozen Embryo Transfer (FET) will be arranged. This will either be in a natural or programmed cycle and your consultant will discuss which might be best for you. The remaining embryos suitable for transfer will remain in frozen storage for future use if you wish. One transfer is included in the PGT-A package, there is an additional cost for subsequent FET cycles PGS. It is important to be mindful that embryos have to be of a certain quality in order to survive the biopsy, freeze and thaw. It may be therefore, that not all of your embryos are suitable for biopsy. Your embryologist will discuss with you on D5 which embryos will be suitable for testing.

It is also possible to test embryos which have already been frozen by thawing them and undertaking the biopsy. The embryo will then need to be re-frozen. There is no evidence to suggest that thawing / re-freezing has a detrimental effect on the embryo although there is always a very small risk of the embryo not surviving a freeze / thaw cycle (approximately 3%). It is only possible to biopsy embryos of a certain quality, it may be that not all the embryos you have in storage are suitable for biopsy, our embryology team will be able to advise which of your embryo(s) is suitable for biopsy.

If there are no embryos suitable for transfer, you will be informed of this at consultation and the future treatment options for you will be discussed. Legally we also need your consent to allow the abnormal embryos to perish. This is included in the PGT-A consent form, but we will confirm with you that you give your consent for this to happen.

At any point you can elect to proceed with an embryo transfer without biopsy. A cancellation fee is applicable, but a refund will be generated for the remaining amount (see Price List).

Studies into PGT-A

Many years ago PGT-A was performed by a technique called FISH (fluorescent in situ hybridisation), which only looked at limited number of chromosomes in the embryo. These early studies were not effective at increasing the likelihood of a live birth. Technology has since improved, and genetics labs are now able to use tests that detect all of the chromosomes and are therefore more effective.

Studies using these new techniques showed that the chances of an embryo with a normal number of chromosomes producing a baby was more than 25% higher than those chosen based on the appearance of the embryo (morphology). While these results are extremely promising, there are still no robust clinical trials that have shown that PGS can significantly increase live birth rates Although there are studies reporting improvements in IVF success rates using PGT-A, there is other research suggesting that chromosome testing is of no benefit. Ultimately it is a selection tool and doesn't change the embryos you start with. Your chance of a livebirth will be the same whether we test the embryos and replace the normal embryos only or whether we don't test and replace one at a time. However, PGT-A may reduce the number of embryo transfers needed and may reduce the risk of miscarriage. There is also data suggesting that PGT-A may be of no benefit to patients with less than 3 embryos suitable for biopsy, although this is always a discussion the embryologist will have with you on the day of biopsy. Because of the lack of robust evidence to support PGT-A it is currently assigned a red traffic light rating by the fertility regulator the HFEA (https://www.hfea.gov.uk/treatments/treatment-add-ons/). For this reason, it is not something that we believe should be offered to everyone but do feel might be helpful in certain groups.

What test results can I expect?

For each embryo one of three results will be obtained (Fig 2):

- The embryo may be **euploid** meaning it carries a normal number of chromosomes, these are the embryos that are ok to be transferred.
- The embryo may be **aneuploid** meaning it carries an abnormal number of chromosomes, it may have an extra chromosome, be missing a chromosome or have an extra set of chromosomes. These embryos would not be considered suitable for transfer as there is a high chance of implantation failure, miscarriage or a chromosomally abnormal baby (in the very unlikely event the pregnancy continues to term) with these embryos.
- The embryo may be a **mosaic**. This means that some of the cells tested have an abnormal number of chromosomes and some have a normal complement of Chromosomes. Mosaic embryos can result in normal pregnancies although pregnancy and livebirth rates are lower with these embryos. It may if there are no euploid embryos that the fertility consultant discusses transfer of a mosaic embryo, you would usually be offered genetic counselling to assist you in making this decision.

In most cases, some embryos will be normal and some will be abnormal. However, there is a chance that none of the embryos will be normal, in which case there will be no embryo transfer.

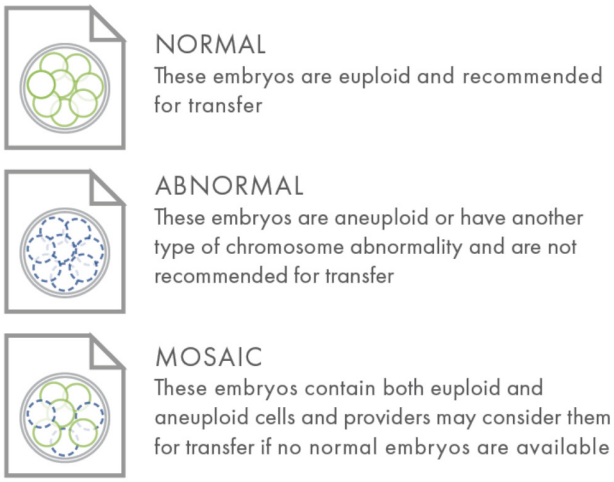


Fig 2 - Provided by Cooper Genomics

Additionally, up to 3% of embryos tested will fail to give a result. This can be due to the chromosomes degrading before testing, or technical errors. Embryos without a result can still be transferred, but it will not be possible to say whether or not they have a correct number of chromosomes.

These tests will only look at the numbers of chromosomes in the embryo and cannot detect genetic disorders. If either partner carries a specific genetic disorder that could impair the normal development of a child affected by the disorder, you will be referred for PGT-M (also known as pre-implantation genetic diagnosis (PGD)). PGT-A cannot screen against genetic disorders and does not guarantee a child will not be born with a genetic disorder (e.g. Cystic Fibrosis) rather than a chromosomal disorder (e.g. Down's Syndrome).

Antenatal Screening

PGT-A is a 'pre-implantation' test which carries a small risk of misdiagnosis. Therefore, if you do become pregnant, conventional 'prenatal' (first trimester) screening is still highly recommended. The intention of the PGT-A is to decrease the risk of transferring an embryo with loss or gain of whole chromosomes. However, technical limitations mean that the detection and transfer of a chromosomally normal embryo cannot be 100% guaranteed, though the risk of misdiagnosis is less than 1%.

Ultrasound and blood markers can be used to assess the likelihood of certain chromosomal abnormalities prenatally. If these results suggest a high risk or you would like certainty regarding the chromosomal content of the pregnancy Chorionic villous sampling

(CVS) or amniocentesis can be undertaken, however these procedures do carry a small risk of miscarriage. Your Obstetrician will be able to discuss these options with you. Non-invasive prenatal test (NIPT) can also be used which is a blood test in early pregnancy. This however, only detects 5 chromosomes so is not as comprehensive as the PGS or CVS/ amniocentesis tests.

What are the risks of having PGT-A?

- **No embryos for biopsy**. There is a chance that no embryos develop on to the blastocyst stage and therefore that there are no embryos for biopsy and transfer. However, it is very likely that embryos that fail to develop to the blastocyst stage would be chromosomally abnormal.
- **Embryo damage**. There is a risk of embryos being damaged during the biopsy process meaning they are not suitable for freezing and transfer. This risk is very small (approximately 2%).
- **No aneuploid embryos**. There is a chance that all the embryos biopsied are aneuploid and therefore that there is no embryo suitable for transfer. This becomes more likely as female age increases.
- **Risk of misdiagnosis**. Unfortunately, tests are rarely 100% accurate and there is a risk of a euploid embryo being incorrectly diagnosed as aneuploid and an aneuploid embryo being diagnosed as being euploid. The chances of this are less than 1%. We would always recommend prenatal screening for chromosomal abnormalities after PGT-A.
- **Risk of no diagnosis/partial diagnosis**. Some embryos may have no diagnosis, due to the absence of chromosomes, or technical difficulties in the fixation process the risk of this is up to 3%. Embryos without a result can still be transferred, but the possible advantages of PGS will not apply. In addition, sometimes the analysis may not be clear for one of the chromosomes tested. Embryos with such partial results may be transferred, but this must be discussed with either a geneticist or a consultant. The risks of having such an embryo back will be explained to you. There may also be the option of retesting the embryo.
- Unfortunately, PGT-A does not guarantee a pregnancy or a healthy live birth nor does it eliminate the risk of miscarriage.

Worldwide several thousand babies have now been born from IVF with PGT-A, with no reported increase of congenital abnormalities above the general population rate of 3-5%.

Alternatives to PGT-A

Alternatives to PGT-A during pregnancy include prenatal screening and testing for abnormalities (blood and ultrasound screening, CVS and amniocentesis). These methods will help to identify pregnancies affected by abnormalities such as Down's syndrome.
Another new test available is the Non-Invasive Prenatal Test (NIPT) which is a simple blood

test, which can detect 5 of the most common chromosome abnormalities. This is done in early pregnancy but again does not increase the chances of a successful pregnancy.

If these tests come back with an abnormality you will be referred to a specialist fetal medicine team who will guide you through your options.

Confidentiality

Confidentiality of your records will be maintained at all times. Only personnel of the genetics laboratory, the staff at BCRM and the Human Fertilisation and Embryology Authority (HFEA) will have access to your records.

Specimen retention

The cells to be tested will be destroyed during the process of the analysis. This will usually occur within 5 days of the biopsy and the DNA will be retained for a minimum of one year. It is important to continue to maintain contact with BCRM and we can report back to the genetics laboratory if there were any abnormalities detected in your pregnancy. If for any reason the PGT-A test is not performed the sample will be destroyed within 60 days of receipt, as stipulated by standard laboratory rules.

Follow-up

If you do not get pregnant after replacement of a normal embryo you will have an appointment with a fertility consultant to discuss your treatment and how you wish to proceed.

If you are pregnant your Midwife will organise the pre-natal testing. If a late-stage miscarriage occurs, we request that chromosome studies be performed on the products of conception. All results from genetic testing of the pregnancy or the child up to the age of 1 should be sent to BCRM so that it can be passed onto the genetics laboratory. This information will remain confidential and will be used to monitor outcomes of the PGT-A program.

BCRM Bristol Centre for Reproductive Medicine

Address

BCRM - Bristol Centre for Reproductive Medicine
135 Aztec West
Almondsbury
Bristol
BS32 4UB

Telephone

0117 259 1159

Email

Contact@BCRM.clinic