PATIENT INFORMATION

Preimplantation Genetic Testing for monogenic / single-gene conditions (PGT-M)

Previously known as Preimplantation Genetic Diagnosis (PGD)

What is PGT-M?

Preimplantation genetic testing for monogenic/single gene condition (PGT-M), previously known as preimplantation genetic diagnosis (PGD) is an embryo genetic test for individuals who know they are at an increased risk of passing on a known genetic condition. PGT-M can be performed on embryos to greatly reduce the risk of having an affected child. PGT-M involves custom designing a test for each couple and their specific genetic change to identify and select unaffected embryos for transfer.

Who is PGT-M for?

PGT-M is available for individuals who are at increased risk of passing on a specific single-gene condition. You may consider PGT-M if:

- You and your partner are known carriers of the same recessive genetic condition (for example cystic fibrosis, spinal muscular atrophy, beta thalassaemia)
- You are a carrier of an X-linked genetic condition (for example Fragile X syndrome, Duchenne Muscular Dystrophy)
- You or your partner have or are at risk of having a single-gene condition (for example Huntington's disease, Marfan syndrome)
- You or your partner have a gene mutation associated with a hereditary cancer syndrome (for example *BRCA1*, *BRCA2*, *TP53*)
- You or your partner have had a child or pregnancy affected with a single gene condition.

What conditions can be tested for with PGT-M?

Monogenic or single gene conditions are genetic conditions caused by mutations or changes in a single gene. These conditions can be inherited in several different ways:

Autosomal conditions occur when there are one or two copies of a gene mutation on any chromosome that is not a sex chromosome.

Autosomal dominant conditions: only one copy of a gene mutation is required to cause disease.

Autosomal recessive conditions: two copies of a gene mutation are required to cause disease.

X-linked conditions occur when there are one or two copies of a gene mutation on the X chromosome.

X-linked dominant conditions: only one copy of a gene mutation on an X chromosome is required to cause disease in both biological males and biological females.

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X-linked recessive conditions: cause disease in biological females if there are two copies of a gene mutation (one on each X chromosome). For biological males, only one copy of the gene mutation is required to cause disease.

Y-linked conditions occur when there is a gene mutation that causes disease on the Y chromosome. These conditions usually affect biological males.

PGT-M is available for most serious, single-gene conditions provided the specific gene mutation in the family has been identified through genetic testing. Importantly, a unique PGT-M test is designed (known as test development or feasibility studies) for each couple, and the availability of PGT-M is dependent on whether a reliable test can be designed for the family's specific gene mutation.

What is the process for including PGT-M in IVF treatment?

If you or your partner has a single-gene condition and would like to include PGT-M in your treatment, you will be referred to the Nº1 Fertility Genetics Department and a Genetic Counsellor will contact you to begin the process. In this initial call, the Genetic Counsellor will gather information about your family history, discuss the PGT-M process and arrange a genetic counselling consultation to discuss PGT-M and the consent process in detail with you.

From there, the genetic counselling team will gather relevant genetic testing reports and submit your case to the laboratory team at CooperGenomics. CooperGenomics will review the submission and perform an initial check that the technology can detect the reported gene mutation. The CooperGenomics team will also determine what is required for test development (ie. which family members' DNA samples will be needed), and clarify how embryo results will be reported. Once confirmed that test development is available for you/your partners' gene mutation, the genetic counselling team will provide you with DNA testing kits so you can send the required DNA samples to the CooperGenomics laboratory for test development.

Approximately 4-6 weeks after your DNA samples arrive in the laboratory, PGT-M test development is expected to be completed. Once completed, the CooperGenomics laboratory will be ready to receive biopsy samples from your embryos.

Embryo biopsies are performed by our experienced Nº1 embryologists on day 5 or day 6 of embryo development. The procedure involves using a fine glass pipette to take a small sample of cells (3-5 cells) from the embryo. Crucially, the cells are selected from the trophectoderm, a part of the embryo that goes on to form the placenta. All embryos that undergo PGT-M are frozen and stored safely in the Nº1 Fertility laboratory for potential future transfer. Embryos tolerate the biopsy and freezing procedures well. The biopsied cells are frozen and sent to CooperGenomics in the UK for PGT-M analysis. PGT-M results are available within 4 weeks from the date of embryo biopsy.

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Importantly, not all embryos are suitable for biopsy. This is due to a variety of factors such as: embryo quality (grade), stage of embryo development, hatching status, and the way in which an embryo is hatching. We encourage you to discuss the biopsy process with the Nº1 Embryology team for additional, specific information about your embryo/s.

For no additional cost, embryos that undergo PGT-M are also analysed for other chromosome abnormalities using PGT-A (please see *Patient Information: PGT-A* for further information).

What is PGT-M test development and how does it work?

Unlike direct gene mutation testing in adults, single-gene genetic testing in embryos involves analysing a very small amount of DNA and requires special techniques to do so. PGT-M is performed using a technique called karyomapping which, compared to older methods, is a faster and more accurate way to design tests for single-gene conditions.

Kayomapping involves identifying 30-50 unique data points surrounding the gene of interest to create a map or “fingerprint” profile for the patient and partner, and one or more family members of known genetic status. Using this technique, the unique DNA “fingerprint” associated with the gene mutation is identified. Embryo(s) can then be tested to determine whether they carry the “fingerprint” associated with the gene mutation, or if the embryo has inherited a normal copy of the gene.

Karyomapping is more reliable than direction mutation testing because instead of using one point of data to identify the presence or absence of the mutation in an embryo, more than 30-50 points of data are used to track the mutation throughout two or more generations. Using this approach means we will always get sufficient data from an embryo to determine its genetic status, and if there is no data available following PGT-M testing, we can be sure the test itself has failed rather than assuming the embryo is unaffected.

What is required for PGT-M test development?

As each PGT-M test is unique and specific to the individual or couples’ family, DNA samples from both partners, and often additional family members of known genetic status will be requested for PGT-M test development. If family members are not available, other test protocols may be used for PGT-M test development.

Moreover, if individuals or their partners are at-risk of having a genetic condition but do not wish to know their genetic status, exclusion testing may be a suitable option.

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What is exclusion testing?

Some people have a parent affected by a serious genetic condition, such as Huntington's disease, that does not become symptomatic until later in life. Individuals in this scenario are 'at risk' of having inherited the genetic condition from their parent, and their embryos are thus 'at risk' of also inheriting the genetic condition. Understandably, some people in this scenario do not wish to have genetic testing themselves to determine if they have inherited the genetic condition, however, may wish to use exclusion testing through IVF to greatly reduce the risk of potentially passing the condition on to their children.

Exclusion testing is an approach that uses PGT-M technology to identify embryos 'at risk' of having the genetic condition without revealing the genetic status of the embryo's parent.

Using this approach, embryos are not tested directly for the gene mutation, but are analysed to determine if they have inherited either copy of the gene of interest from the family member affected by the genetic condition.

Exclusion testing means that the number of embryos available for transfer will be reduced. On average, up to 50% of excluded 'at risk' embryos are expected *not* to carry the mutation, however will be unsuitable for transfer due to results indicating 'at risk' status. The advantage of exclusion testing, however, is that it does not reveal the 'at risk' parent's genetic status.

How are PGT-M results reported?

You will be contacted by a Nº1 Genetic Counsellor to discuss your PGT-M results. PGT-M results are expected within 4 weeks from the date of biopsy and are reported as 'affected', 'unaffected' and in cases involving X-linked recessive or autosomal recessive conditions, 'carriers' are reported. Included PGT-A results are reported at the same time, as either 'euploid/normal', 'aneuploid/abnormal', 'mosaic' (please see *Patient Information: PGT-A mosaic result* for further information) or 'no result' (please see *Patient Information: PGT no result* for further information).

How accurate is PGT-M?

The accuracy of PGT-M is over 95%, however may vary depending on the specific single-gene condition being tested. More detailed information about your PGT-M test becomes available from CooperGenomics once the case has been accepted and test development is completed.

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Why do we use CooperGenomics?

CooperGenomics have multiple genetic testing laboratories in both USA and UK. They are a global leader in reproductive genetic testing. We have used their services and expertise since the start of Nº1 Fertility and to date, they have performed over 100,000 embryo testing procedures.

What is the cost of PGT-M?

Currently, PGT-M test development costs $1815. The cost of PGT-M testing per embryo (including PGT-A) costs $780 and is capped at 6 embryos per cycle ($4250). For example, if you were able to biopsy 8 embryos in one cycle, it would be capped at the cost of 6 embryos. Rebates are available for PGT-SR and any eligible rebates will be applied to your PGT invoice.

What are the risks and limitations of PGT-M?

Every embryo biopsy procedure carries a small risk of damage to the embryo, and in rare circumstances loss of the embryo. Additionally, not all embryos are suitable for biopsy. The experienced Nº1 Embryology team make careful and educated decisions regarding an embryo's suitability for biopsy to preserve the embryo's viability.

Due to testing and process limitations, not all embryo biopsy samples return a PGT-M result. These embryos are reported as 'no result' (please see *Patient Information: PGT no result* for further information).

Embryos with affected PGT-M results are unsuitable for transfer.

Importantly, included PGT-A is a screening test, not a diagnostic test. This is largely because we are analysing a small number of cells destined to become the placenta from an embryo with approximately 100 cells. This means we cannot clarify the chromosomal composition of a whole embryo. However, PGT-A offers the best estimate available. Because PGT-A is a screening test, we would recommend NIPT (non-invasive prenatal testing) for a pregnancy achieved with a PGT-A tested embryo.

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What can't PGT-M test for?

PGT-M cannot test for small chromosome abnormalities, potential birth defects or unknown single-gene conditions. For example, some individuals can be at risk of having a child with a genetic condition because they are carriers for a recessive condition such as cystic fibrosis, Fragile X syndrome and spinal muscular atrophy. Genetic carrier screening is available to determine if you and your partner are 'silent carriers' of any recessive genetic conditions and clarify if you are at risk of having a child with a recessive genetic condition. Some conditions are not caused by genetic factors or may involve a mixture of genetic and non-genetic factors such as spina bifida, autism spectrum disorder and intellectual disability. Such conditions are unable to be tested using PGT-M.

If you are concerned about your family history or specific medical or genetic conditions, please get in touch with Nº1 Genetics Department.

Does PGT-M replace prenatal testing?

No. While transferring a PGT-M unaffected or carrier embryo is expected to significantly reduce the risk of having a child affected with the condition, it does not eliminate this risk.

It is recommended to consider prenatal testing options if a pregnancy is achieved following transfer of a PGT-M tested embryo. There are two diagnostic prenatal tests which can include single-gene testing:

> *Chorionic villus sampling (CVS)* is an invasive diagnostic test performed at approximately 12 weeks gestation. This specialised test involves taking a small sample of placental tissue via ultrasound-guided needle. DNA analysis of a CVS sample can provide diagnostic information about the single gene status and chromosome complement of a pregnancy. CVS procedures are performed by experienced specialist doctors, however there is approximately 1 in 500 risk of procedure-associated miscarriage.
>
> *Amniocentesis* is an invasive diagnostic test performed at approximately 16 weeks gestation. This specialised test involves taking a small sample of amniotic fluid via ultrasound-guided needle. DNA analysis of an amniocentesis sample can provide diagnostic information about the single gene status and chromosome complement of a pregnancy. Amniocentesis procedures are performed by experienced specialist doctors, however there is approximately 1 in 1000 risk of procedure-associated miscarriage.

Additionally, NIPT (non-invasive prenatal testing), a chromosome screening test performed at approximately 10 weeks gestation, is recommended for pregnancies achieved with PGT-M embryos to screen for chromosome abnormalities.

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Questions?

If you have read this information and wish to discuss PGT-M further, please contact the Nº1 Genetics Department on 9132 9600 or email genetics@number1fertility.com to organise a time to speak to one of our Genetic Counsellors.

The information provided above is intended for educational purposes only and should not be used as a substitute or replacement for medical advice received from a medical professional. It is important to discuss your individual circumstances and situation with your treating doctor.

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