PATIENT INFORMATION

Preimplantation Genetic Testing for Structural Rearrangements (PGT-SR)

What is PGT-SR?

Preimplantation genetic testing for structural rearrangements (PGT-SR) is an embryo genetic test that can be performed to determine if an embryo has inherited a balanced or unbalanced form of a chromosome structural rearrangement. PGT-SR screens embryos for their chromosome quantity. Chromosome structural rearrangements are changes from the normal size or arrangement of chromosomes, which are structures that contain all our genetic material. Individuals with structural chromosome rearrangements are at an increased risk of producing embryos or conceptions with extra or missing genetic material, also referred to as unbalanced embryos. Embryos or conceptions with unbalanced chromosomes typically do not lead to successful pregnancy. The aim of PGT-SR is to determine which embryos have balanced chromosomes and selecting for transfer these 'balanced' embryos with the highest chance of success.

What are chromosomes and why are they important?

We are all made of billions of cells, and inside each cell is DNA. DNA is packaged into larger structures called chromosomes, that each contain thousands of genes. Genes provide specific instructions for our body to grow, develop and function.

Chromosomes come in pairs and are numbered by size from 1 through to 22. The 23rd pair are the sex chromosomes that typically determine our biological sex. Usually, two X chromosomes (XX) are found in biological females, and one X and one Y (XY) are found in biological males. We inherit one copy of each chromosome from an egg and one from a sperm, to total 23 pairs (46 total) of chromosomes. Most cells in our body contain a full set of 23 pairs of chromosomes, and each chromosome contains genes essential for our growth, development, and healthy function.

Structural rearrangements of chromosomes can occur during egg and sperm development or be inherited from one or both parents. Individuals with structural chromosome rearrangements are at an increased risk of producing embryos or conceptions with extra or missing chromosome material, which typically do not lead to a successful pregnancy. Approximately 50% of all miscarriages are considered to be the result of abnormal or unbalanced chromosomes. Importantly, structural rearrangements are not always passed on, and it is possible for a person who carries a structural rearrangement to have healthy children with balanced chromosomes.

What are structural rearrangements and how do they impact fertility?

Observed in approximately 1 in 200 to 1 in 500 people, structural rearrangements are changes to the normal size and/or arrangement of chromosomes that can cause subfertility. In IVF, we typically see healthy individuals who carry *balanced* chromosome structural rearrangements.

These individuals are healthy because a balanced chromosome rearrangement means there has been an even exchange of chromosome material between chromosomes, and thus there is no extra or missing genetic information that could cause health problems. Most carriers of

balanced structural rearrangements are unaware of their carrier status until they begin trying to have a baby. Chromosome structural rearrangements are more common findings in the infertility setting, compared to the general population.

The two most common balanced structural rearrangements we see in IVF are called translocations and inversions. Translocations are structural chromosome abnormalities that occur when different chromosomes break and re-join together in a different order. There are two different types of balanced translocations: reciprocal and Robertsonian translocations.

Reciprocal translocations occur when two different chromosomes break and exchange segments with no apparent loss or gain of genetic information.

Robertsonian translocations occur when two chromosomes join to form one larger chromosome, resulting in an overall chromosome number of 45 (22 pairs plus the translocated chromosome) instead of 46 (23 complete pairs of chromosomes).

Inversions occur when a single chromosome breaks in two places, and the broken segment is flipped and reinserted upside down back into the same position.

If a parent or donor carries a structural rearrangement, it is possible for created embryos to inherit a balanced or unbalanced quantity of chromosomes. Each embryo may have either a normal, balanced quantity of chromosomes; an unbalanced quantity of chromosomes; or a balanced rearrangement of chromosomes like the parent or donor with the structural rearrangement.

How are structural rearrangements identified?

As part of your initial screening, your Fertility Specialist will arrange karyotype testing for both gamete providers. Karyotype testing determines the number of chromosomes in your cells, can identify extra or missing chromosome material, and if there is a structural rearrangement. If you are found to carry a structural chromosome rearrangement, your Fertility Specialist along with the Nº1 Genetic Counselling team will discuss this with you to help you to understand your result. You will be offered an appointment with a Nº1 Genetic Counsellor who can discuss the implications of your result and the genetic testing options available to you. One of these options is PGT-SR.

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Who is PGT-SR for?

You may consider PGT-SR if you or your partner are a carrier of a chromosome structural rearrangement, or if you have had a child or pregnancy with a chromosome structural rearrangement.

What is the PGT-SR process?

If you decide to proceed with PGT-SR, we will arrange a genetic counselling consultation and your case will be reviewed by our external genetics laboratory, CooperGenomics. CooperGenomics perform an initial analysis to determine if the PGT-SR technology can detect the chromosome structural rearrangement in embryos. Once your case is accepted by CooperGenomics, they will be ready to accept 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) 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-SR 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 our external genetic testing laboratory CooperGenomics in the UK for analysis. PGT-SR results are available within 2-4 weeks from the date of embryo biopsy.

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.

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

How is PGT-SR performed on embryos?

The embryo biopsy samples are sent to our external genetic testing laboratory CooperGenomics in the UK. The DNA is extracted from the sampled cells, then copied millions of times for chromosome analysis. Sensitive DNA testing techniques called Next Generation Sequencing (NGS) are used to develop a profile of the chromosomes in the sample. The chromosome profile of the embryo is compared to a standardised set of reference chromosomes to identify if there is an imbalance in the quantity of chromosomes and determine whether the embryo has inherited an unbalanced form of the structural rearrangement. PGT-SR results are reported as ‘balanced’ or ‘unbalanced’ as the technology cannot distinguish between embryos with a normal, balanced quantity of chromosomes, or embryos that carry the same balanced structural rearrangement of chromosomes as the parent or donor.

How accurate is PGT-SR?

The accuracy of PGT-SR is over 97%.

How are PGT-SR results reported?

You will be contacted by a Nº1 Genetic Counsellor to discuss your PGT-SR results. PGT-SR results are available within 2-4 weeks from the date of embryo biopsy. PGT-SR results are reported as 'balanced' or 'unbalanced' for the structural rearrangement. 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).

Why do we use CooperGenomics?

CooperGenomics have multiple genetic testing laboratories in both the 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-SR?

Currently, the cost of PGT-SR (including PGT-A) is $780 per embryo and is capped at $4250 per cycle for 6 or more embryos. For example, if you were able to biopsy 8 embryos in one cycle, it would be capped at $4250. 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-SR?

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-SR result. These embryos are reported as 'no result' (please see *Patient Information: PGT no result* for further information).

Embryos with unbalanced PGT-SR results are unsuitable for transfer.

Importantly, the included PGT-A analysis 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 pregnancies achieved with 'normal' PGT-A embryos.

What can't PGT-SR test for?

PGT-SR cannot test for specific genetic conditions. Sometimes individuals can be at risk of having a child with a genetic condition because they are 'silent carriers' for a recessive condition, or they have a family history of a known genetic condition. As PGT-SR screens for chromosome quantity in an embryo only, it does not test for specific gene changes associated with genetic diseases. 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. Reproductive 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-SR.

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

Does PGT-SR replace prenatal testing?

No. While transferring an embryo that has tested balanced with PGT-SR is expected to significantly reduce the risk of having a child with a chromosome abnormality, it does not eliminate this risk. NIPT (non-invasive prenatal testing) is recommended for a pregnancy achieved with a PGT-SR tested embryo.

Questions?

If you have read this information and wish to discuss PGT-SR further, please contact the Nº1 Genetics Department on 03 9132 9609 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.