Informed Consent for Pre-Implantation Genetic Testing for Structural Rearrangements (PGT-SR) and Aneuploidy (PGT-A) – Primary Outcomes and Secondary Outcomes

Female patient full name:	
Female patient Date of Birth:	
Clinic ID (female patient):	

Partner full name (if applicable):	
Partner Date of Birth (if applicable):	
Clinic ID (partner):	

This consent is intended for patients who are planning to undergo in vitro fertilization (IVF) treatment and want Preimplantation Genetic Testing (PGT) to be performed on cells (biopsies) taken from their embryos. Juno Genetics UK Ltd. (Juno Genetics) is the clinical diagnostic laboratory that will receive the biopsies from the embryos and will perform PGT. A separate consent form regarding the embryo biopsy procedure should be provided by the IVF clinic/laboratory performing the biopsy. Juno Genetics recommends that genetic counselling be offered to the patient(s) prior to signing this form.

What is PGT-SR?

PGT-SR is a method that aims to identify whether an embryo has the correct amount of chromosomal material. Chromosomes are minute, rod-like structures, which exist inside cells. The chromosomes are made of DNA and carry the instructions (genes) needed for an embryo to develop normally. Human beings typically have 46 chromosomes, including two X chromosomes in the case of biological females (46,XX) or one X and one Y chromosome for biological males (46,XY). Some people are balanced carriers of a chromosomal 'translocation' or an 'inversion', which means that pieces of their chromosomes have changed positions with respect to each other. Such individuals are at increased risk of producing embryos with an incorrect amount of chromosomal material in their cells (unbalanced). Embryos with losses or duplications of pieces of chromosomes (unbalanced) have increased risks of failing to implant in the uterus, miscarrying or producing a child with a genetic abnormality (such abnormalities may cause a range of health problems, learning disabilities and complex developmental needs). PGT-SR seeks to test the embryos produced during an IVF cycle, distinguishing those with abnormal amounts of chromosomal material (unbalanced) from those where the chromosomes are either entirely normal or balanced - where the rearrangement is present, but no pieces of chromosome have been lost or duplicated (a situation similar to the parent who carries the translocation or inversion). Embryos that are predicted to have a low risk of an incorrect amount of chromosomal material can be prioritised for transfer to the uterus. In addition to in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI), PGT-SR involves the removal of a few cells from each embryo (biopsy) and cryopreservation (freezing) of the embryo. The cell samples are sent to Juno Genetics where analysis of the chromosomes is carried out. Importantly, the actual embryos do not leave the IVF clinic. Alternatives to PGT-SR include conceiving naturally and opting for a genetic test during pregnancy, for example amniocentesis or chorionic villus sampling.

It is crucial that unprotected sexual intercourse is avoided from 15 days prior to egg collection until after the pregnancy test, carried out approximately two weeks after transfer of embryos to the uterus. Sexual intercourse within this time could lead to an untested embryo producing a pregnancy, which might have an abnormal number of chromosomes.

When PGT-SR is carried out, a second test known as PGT for aneuploidy (PGT-A) is simultaneously undertaken. PGT-A analyses all the chromosomes, not just the ones indicated for PGT-SR, in order to identify whether an embryo has the correct number of chromosomes. Embryos with an incorrect number of chromosomes have increased risks of failing to implant in the uterus, miscarrying or producing a child with a genetic abnormality (for example, Down syndrome). PGT-A can potentially reduce these risks by helping to distinguish embryos with the right number of chromosomes from those that have either too many chromosomes or too few. Embryos predicted to have a low risk of a chromosome abnormality can be prioritised for transfer to the uterus.

Risks and limitations of PGT-SR

- There is a chance that no chromosomally normal embryos will be produced in a cycle of IVF and PGT-SR. In such cases, no embryos will be transferred.

- PGT-SR will detect most losses and gains of chromosomes, including chromosomes that are not involved in the rearrangement. However, PGT-SR cannot detect all forms of chromosome abnormality and for this reason, prenatal testing is recommended to confirm that any pregnancy established after PGT-SR is chromosomally normal.
- The accuracy of PGT-SR is dependent on the genetic information provided to Juno Genetics in the medical records and genetic test reports. The information provided to Juno Genetics is evaluated in order to determine if the PGT-SR method would be able to detect unbalanced products of the rearrangement. Incorrect definition of chromosomal breakpoints and/or errors in the family history information provided to Juno Genetics may affect the ability of the PGT-SR test to detect the unbalanced products of the rearrangement.
- While losses and duplications of pieces of chromosome can usually be detected within embryos, it is not possible to distinguish embryos that have a balanced form of the rearrangement (the same situation as the parent who carries the rearrangement) from those with an entirely normal set of chromosomes. This is because in these two situations the amount of chromosomal material is the same.
- Since PGT-SR only looks for abnormal numbers of chromosomes, it cannot exclude the possibility that an embryo could have other types of genetic abnormalities and/or birth defects, which PGT-SR does not detect. In the general population, there is a 3-5% risk that a child will be born with a birth defect or intellectual disability due to genetic and/or non-genetic causes. The use of PGT-SR does not reduce that risk.
- PGT-SR minimises the possibility of transferring an embryo with an abnormality related to the specific chromosome rearrangement under investigation. As with every medical testing technique, PGT-SR has a margin error, estimated to be 1-2%. Therefore, any pregnancy obtained following PGT-SR must not exclude the usual prenatal evaluation advised for pregnant woman at elevated risk of a genetically abnormal pregnancy.
- While very unlikely, there is a chance that a biopsy sample could be lost or damaged due to a problem within the laboratory or during transportation. In such cases, the number of chromosomes in the cells of the embryo remains unknown. Juno Genetics only assumes responsibility for embryo samples once they arrive at its laboratory.
- There is a chance that Juno Genetics will be unable to obtain a result from a biopsy sample (this can happen if the cells removed from the embryo contain degraded DNA, as well as for other reasons). This occurs in approximately <5% of samples.
- Testing is performed on a sample of cells from the embryo, and while it is expected that these cells are the same as the remainder of the cells in the embryo, there is a possibility they are different.
- PGT-SR offers no guarantee that pregnancy will occur or that a healthy child (free from all genetic or non-genetic defects) will result.
- With any procedure involving handling of microscopic material, human error can occur, although steps are taken in the laboratory to minimise such risks.
- Like many techniques, PGT-SR depends upon equipment. Equipment failure and other problems such as loss of power and natural disasters can potentially occur, resulting in failure to obtain PGT-SR results and loss of samples.
- PGT-SR involves the testing of a small number of cells from each embryo. There is a small chance of contamination with cells or genetic material from other sources. This is a risk of the procedure and, if this occurs, it may result in an incorrect analysis or a failure to obtain a result.

Possible embryo classifications in PGT-SR cases include:

- Negative/Balanced: Embryos in which the biopsy sample is predicted to have a normal chromosome number (46,XX or 46,XY) or a balanced chromosomal rearrangement. Please note, the test does not distinguish between embryos with an entirely normal set of chromosomes and those that have the rearrangement in a balanced form.
- Positive (for full chromosomal aneuploidy): Embryos in which the biopsy sample is predicted to have an abnormal number of chromosomes. These embryos are considered to be at high risk of chromosomal abnormality.
- Positive/Unbalanced (for structural rearrangement aneuploidy): Embryos that have inherited an unbalanced form of the chromosomal rearrangement. These embryos have gains and/or losses of chromosomal fragments related to the rearrangement carried by the patient.
- Mosaic: Embryos where some cells in the biopsy specimen have a 'normal' (46,XY/46,XX) number of chromosomes while other cells have an abnormal number of chromosomes.
- No result: No prediction could be made concerning the chromosomal status of the embryo. This can be caused by a failure to amplify DNA in the biopsy specimen, contamination of the specimen with DNA from another source, and various other technical problems. In such cases, a second biopsy is recommended, provided the embryo is sufficiently developed.

Mosaicism: Secondary finding of uncertain significance

This testing may detect secondary finding of uncertain significance, which include results suggestive of the presence of a mixture of normal and abnormal cells (mosaicism). At this time, the clinical significance of these findings is not well understood. According to current scientific evidence, embryos with apparent mosaicism in the biopsy sample have a capacity to implant and produce a child as embryos without mosaicism.
For the PGT-A/SR reports including primary+secondary outcomes, mosaic results will be included in the final PGT report.

Publications and research

The information regarding your participation in PGT will be kept confidential except if it is required by law or by regulatory bodies. However, in some scenarios the data obtained from your embryos may be published to help advance knowledge in the fields of assisted reproduction and genetics. Such information will not identify. Results from multiple individual patients/embryos is usually grouped together anonymously.

Your samples

All samples will be kept for 5 years before being discarded. In this time, any leftover material from the cells taken from each embryo may be used for training and quality assurance purposes. If you wish to have your samples discarded sooner, please contact the laboratory.

We request that you allow Juno Genetics to use surplus DNA from embryo biopsy specimens to assist in the development of new and/or improved genetic tests. Such DNA is leftover after PGT has been completed. The use of this surplus material has no effect on the treatment you receive and is carried out in an anonymised manner (all personal identification is removed from the sample). Please confirm whether you agree to your leftover samples being used to help Juno Genetics to train staff and create new tests.

☐ **Yes**
☐ **No**

I/we give permission for any surplus DNA, remaining after completion of PGT-SR testing, to be used for research and the development of new tests. I understand that before any research takes place, all identifying information will be removed from the sample(s).

By signing this form, you are agreeing to the following statements:

- I/We have/had the opportunity to discuss with my/our physicians or genetic counsellors the meaning of pre-implantation genetic testing, the risks and benefits of the testing, as well as the alternatives (and the risks and benefits which accompany such alternatives). I/We understand that this process requires that an embryo biopsy be performed at our IVF centre and that subsequent PGT will performed at Juno Genetics UK Ltd. Juno Genetics has strongly recommended that we discuss all of the potential limitations and outcomes with a genetic counsellor.
- I/We have considered the options and weighed the risks and benefits. I/we understand that there is potential for PGT-SR to be unsuccessful in giving a result and that there is a small possibility for an embryo classified 'negative/balanced' using PGT-SR to be affected by a chromosome abnormality.
- I/we understand that PGT-SR does not completely remove the risk of having a pregnancy affected by a genetic disorder. I/we understand that prenatal testing (amniocentesis or chorionic villus sampling) is recommended in the event of a pregnancy and I/we can discuss this with a genetic counsellor.
- I/we understand that I/we are voluntarily using this test and may withdraw from the testing at any time by notifying the laboratory in writing of my/our intention to withdraw, and that I/we may withdraw my/our consent to any procedure at any time.

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Female patient's Signature **Date**

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Partner's Signature (if applicable) **Date**

The above patient(s) have been counselled by me and others with respect to the risks and benefits of the various options. The patient(s) appeared capable of understanding the information presented as demonstrated by the discussion and their participation.

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Clinician/ Genetic Counsellor Name (if applicable)

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Clinician/ Genetic Counsellor Signature **Date**