Informed Consent for Preimplantation Genetic Testing for Monogenic Disorders (PGT-M) and Aneuploidy (PGT-A) – Primary 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.

Background information (PGT-M)

PGT-M is a method that examines embryos produced during an IVF cycle in order to assess their risk of having alterations of the genetic code associated with a specific genetic disorder. In most cases, these changes in an embryo's genetic code (mutations) are inherited from one or both of their parents. PGT-M enables embryos that have inherited mutations responsible for a particular disorder to be distinguished from those predicted to be at low-risk of the condition. Only embryos estimated to be at low-risk are considered for transfer to the mother's uterus and, for this reason, the chance of having a pregnancy with a fetus affected by the condition is expected to be lower than would be achieved without PGT-M.

Since every family is unique, PGT-M is designed to analyse the specific gene(s) and the change(s) to the sequence of the DNA that are relevant to each of them. The first step is for the Juno Genetics laboratory to create a customised test tailored to the needs of the patient(s) who requested PGT-M. Once the genetic test has been shown to work, the IVF cycle can proceed. In general, the IVF process involves ovarian stimulation with the aim of producing several eggs, retrieval of the eggs and their fertilisation with sperm. The embryos produced are grown in the IVF clinic and when they are between five and seven days old, embryologists remove (biopsy) a small number of cells from each of them (except for embryos that are no longer considered viable). The embryos are then cryopreserved (frozen) and will remain at the IVF clinic, while the biopsied cells are sent to Juno Genetics for genetic testing.

Background information (PGT-A)

When PGT-M is carried out, a second test known as PGT-A is also undertaken. PGT-A aims to identify whether an embryo has the correct number of chromosomes. Chromosomes are minute, rod-like structures, that 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. 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.

Important considerations for PGT

For PGT-M, it is recommended that eggs are fertilised using intracytoplasmic sperm injection (ICSI) to reduce the chances of contamination with DNA that does not come from the embryo.

An alternative to PGT-M is to conceive naturally (or use IVF if there is a fertility problem) and then have a genetic test during pregnancy, for example amniocentesis or chorionic villus sampling. Such tests can reveal whether the fetus has the inherited condition.

It is crucial that unprotected sexual intercourse is avoided from 15 days before the 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 fertilisation of an egg, and the possibility of an untested embryo producing a pregnancy, which might be affected by the genetic disorder.

Risks and limitations of PGT-M and PGT-A

- The PGT carried out only focuses on the specific disorder(s) that Juno Genetics was asked to detect and does not reduce the risk of other inherited conditions, nor other congenital or genetic abnormalities that might affect the embryos. Furthermore, PGT-M only examines embryos for the specific genetic variant(s)/mutation(s) that Juno Genetics has been informed about and asked to look for. Consequently, any other genetic variant(s)/mutation(s) that could be associated with the disorder will not be tested and will therefore not be detected.
- There is a chance that all of the embryos produced in a cycle of IVF are affected by the disorder being tested or are chromosomally abnormal, in which case none of them will be suitable for transfer to the uterus.
- Not all genetic variants are amenable to PGT-M. Some disorders are caused by genetic variants/mutations that cannot be detected using the methods currently available at Juno Genetics. If Juno Genetics is requested to carry out PGT-M for a mutation/variant which is unlikely to be detectable for technical reasons, this will be made clear before the IVF cycle is started.
- The customised genetic test depends on the accuracy of the information provided to Juno Genetics in the clinical reports received. Any changes to those reports must be communicated to Juno Genetics so that the testing can be updated if necessary. Failure to communicate this information could impact the accuracy of the test. Similarly, for accurate PGT-M, it is necessary that family relationships, and the disease status of individual family members, are accurately described.
- Juno Genetics will not make any attempts to confirm that the genetic variants/mutations screened are responsible for the disorder. Juno Genetics relies upon the characterisation of the variants/mutations provided by the genetic laboratory that originally identified them in the family.
- This testing may examine DNA sampled from several family members (for example, children, parents, grandparents). This has the potential to reveal instances of non-paternity, if any exist. The presence of non-paternity, or the incorrect communication of other family relationships, can interfere with the ability to accurately develop a genetic test.
- Any history of stem cell or bone marrow transplant in individuals who provide a sample to assist with the development of the PGT-M method should be reported to Juno Genetics, as it could lead to inaccurate genetic results when the embryo(s) are tested.
- PGT-A cannot detect all forms of chromosome abnormality. For example, loss or duplication of pieces of chromosomes (segmental aneuploidy), rather than whole chromosomes, are not always detected.
- There is a 3-5% risk in the general population of having a child with a birth defect or intellectual disability due to genetic and/or non-genetic causes. The PGT-A and PGT-M undertaken does not reduce that risk.
- For abnormalities involving the loss or duplication of whole chromosomes, PGT-A is more than 98% accurate. However, there remains a small chance that an embryo classified 'negative' following PGT-A could still have an incorrect number of chromosomes. Prenatal testing is advisable to confirm the status of any 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 chromosomal and genetic status of the embryo remains unknown. Juno Genetics only assumes responsibility for embryo samples once they arrive at its laboratory.
- Testing is performed on a sample of cells from the embryo, and while it is expected that these cells are genetically the same as the remainder of the cells in the embryo, differences are possible, especially with respect to the presence of chromosome abnormalities.
- With any procedure involving handling of microscopic material, human error can occur, although steps are taken in the laboratory to minimise such risks. A prenatal test (amniocentesis or chorionic villus sampling) can confirm whether or not a fetus is affected by a genetic condition.
- Like many techniques, PGT-A and PGT-M depend upon equipment. Equipment failure and other problems such as loss of power and natural disasters can potentially occur, resulting in failure to obtain results and loss of samples.
- PGT -A and PGT-M involve the testing of a small number of cells from each embryo (embryo biopsy). 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.
- Although the genetic tests are highly accurate, there still remains a risk of inaccurate results. For PGT-A and PGT-M, the risk for misdiagnosis due to a false positive or false negative is estimated to be 2-3%. In addition, there is a

chance (2-4%) of not getting a definitive result for some or all embryos. This can happen if the cells removed from the embryo contain degraded DNA, as well as for various other reasons.

PGT-M Results:

- The PGT-M results will be reported as either positive or negative for the tested variant(s)/mutation(s)/haplotype(s) and the reporting terminologies may differ between cases depending on the specific details of the genetic condition being tested as well as the family history.

  The accuracy of PGT-M is typically between 97-98%, assuming all the medical and biological information about the family has been reported correctly to Juno Genetics. The accuracy for testing will be stated in a letter issued when the development of the customised test has been completed.

PGT-A Results:

Possible embryo classifications after PGT-A include:

- Negative: No abnormalities involving loss or duplication of whole chromosomes or parts of chromosomes were detected in the biopsy sample. The embryo is predicted to have a normal number of chromosomes.
- Positive (for full chromosomal aneuploidies): Embryos in which the biopsy sample is predicted to have an abnormal number of chromosomes. This may involve loss or duplication of whole chromosomes or pieces of chromosome. These embryos are considered to be at high risk of chromosomal abnormality.
- 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 chromosomes in 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 may be undertaken provided the embryo is sufficiently developed, potentially allowing PGT-A results to be obtained.

Incidental findings

Occasionally, PGT-A results may indicate the presence of a chromosome abnormality in one of the two parents, such as a chromosome rearrangement (translocation or inversion) or extra/missing chromosome material (microduplications/microdeletions). If results are suggestive of a parental chromosome abnormality, additional testing may be recommended. The PGT-A method alone, cannot be used to detect all possible parental chromosome abnormalities. If identified during testing, copy number gains and losses above 3Mb will be reported, however this is at the discretion of the Clinical Laboratory Director since some gains/losses are of no clinical significance or are likely to be benign.

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 reports including primary+secondary outcomes, mosaic results will be included in the final PGT-A 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 you. In most cases, results from multiple individual patients/embryos is grouped together anonymously.

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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 create new tests.

☐ **Yes**
☐ **No**

I/we give permission for any surplus DNA, remaining after completion of PGT-M/-A 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 and staff 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 are aware that PGT cannot guarantee that any tested embryo is completely free from genetic defects and understand and accept that there is a chance that an embryo predicted to be unaffected by a specific genetic condition could still lead to pregnancy and/or birth of a child affected by the condition. I/We hereby acknowledge that the information detailed above has been explained to me/us and that I/We consent to the procedures described.
- I/We understand that I/we 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.
- I/We understand that should this process lead to a viable pregnancy, it is recommended that follow-up diagnostic testing (such as amniocentesis or chorionic villi sampling) be performed to obtain fetal cells for genetic analysis and that such tests offer the ability to confirm the PGT results, as well as having the potential to reveal additional genetic conditions not tested by PGT. While PGT may reduce the risk of a specific inherited condition or genetic abnormality the possibility of an affected pregnancy and/or the birth of an affected child cannot be entirely avoided.
- I/We have had a full opportunity to have all of our questions answered and give this consent freely, without coercion or pressure of any kind, based upon all of the information we have considered.

_____ _____

Female patient's Signature **Date**

_____ _____

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)

_____ _____

Clinician/ Genetic Counsellor Signature **Date**