Preimplantation Genetic Testing for a Monogenic Gene Defect (PGT-M) Consent for Single Gene Disorders

Please review this consent and discuss any questions with your medical providers.

PURPOSE

Preimplantation Genetic Testing for a Monogenic Gene Defect (PGT-M), previously known as PGD, for single gene disorders is used to test embryos for a specific genetic disorder prior to implantation.

BACKGROUND

Each cell in the body has chromosomes which are organized structures that contain DNA and proteins. In humans there are 24 different types of chromosomes, designated 1-22 and the sex chromosomes X and Y. Most cells contain 46 total chromosomes, a pair of chromosomes 1-22, and XX for a female and XY for male. The sperm and the egg should each have a set of 23 chromosomes. Therefore, when a sperm fertilizes an egg, the resulting embryo has a total of 46 total chromosomes.

Each woman can produce chromosomally abnormal eggs and each man can make chromosomally abnormal sperm. If an egg with 24 chromosomes is fertilized by a sperm with 23 chromosomes, the resulting embryo contains 47 chromosomes (one extra chromosome). A common example of a chromosome abnormality is Down syndrome, which is caused by three copies of chromosome 21 instead of two. Extra or missing chromosomes, called aneuploidy, can originate from an abnormal egg, abnormal sperm, or a later error in cell division. The abnormalities can result in a spontaneous miscarriage, stillbirth, or child with abnormalities.

Chromosomes are comprised of molecules called DNA. Our DNA is organized into small fragments called genes. There are about 20,000 genes in humans, all of which influence our growth and development. Just like chromosomes come in pairs, most genes also come in pairs, one from the egg and one from the sperm. When the function of a gene is altered by a change (called a mutation) in the specific sequence, a genetic disease results. These mutations can be transmitted in families from generation to generation, or can occur spontaneously in an individual *(de novo).*

Genetic diseases can be inherited in a few different ways. A dominant genetic mutation, if found in one copy of a gene, is enough to cause the disease. The risk for a parent with the dominant disease to pass the condition on to a child is 50%. A recessive genetic mutation causes a disease only when the mutation is in both copies of the same gene. A carrier of a recessive genetic disease has one normal copy of the gene and one copy with a mutation. The majority of carriers are healthy since having one normal copy is typically enough to prevent the disease. Two carrier parents have a 25% risk to have a child with the genetic disease. Sex-linked genetic diseases are caused by mutations on the X or Y chromosomes. Sex-linked diseases can be dominant or recessive and affect males and females differently. The risk for a mother who is a carrier of a recessive sex-linked disease to have a son with the condition is 50%.

PROCEDURES

The PGT-M process is comprised of five main steps. Your local fertility center will perform the first three steps: *in vitro* fertilization, embryo biopsy, and cell preparation. Then the biopsied cells are transported to Igenomix Genetic Services Canada Inc. ("**Igenomix Canada**"), where the analysis is performed. Igenomix Canada may provide biopsy and cell preparation support to your fertility center.

In vitro fertilization (IVF):

PGT-M requires cells from embryos to analyze, therefore, an *in vitro* fertilization cycle is required regardless of fertility history. Your local fertility center will advise you on this process and may require a separate consent. ICSI (intracytoplasmic sperm injection) as a method of fertilization is recommended, but not required prior to PGT-M. If ICSI is not performed, there is an increased risk of "no results" on one or more samples due to contamination of the sperm.

Embryo biopsy:
Embryo biopsy is performed on Day 5 and/or Day 6 of embryo development when the embryo is a blastocyst, called trophectoderm biopsy. A trophectoderm biopsy involves the removal of several cells from each blastocyst. Due to the time required for results, the embryos must be frozen prior to receiving results, called embryo vitrification.

Cell preparation:
The cells are then washed to remove any potential sources of contamination and transferred into a small tube supplied by Igenomix Canada.

Transport:
The tubes with the cells will be transported to the laboratory by courier. Depending on location, the samples may arrive the same day or the next day.

Analysis:
Once the cells are received by the laboratory, the genetic information in the cells is amplified to increase the amount of material present to evaluate. The PGT-M test designed in advance is then run. The test will include detection of presence or absence of the familial mutation(s) and evaluation of markers. Markers are regions with variable sequences that are within or closely linked to the gene of interest. If possible these markers are traced through the family in advance, so it is known which markers are linked with the disease causing gene and which are not. The markers are used as a double check to the mutation result. Embryos without the mutation are considered normal and recommended for transfer. If testing is being performed for a recessive disease and a single mutation is identified, the embryo is classified as a carrier and can also be considered for transfer. Results are forwarded directly to the referring fertility clinic.

Abstinence from intercourse is recommended for two weeks prior to egg retrieval until the pregnancy test. It is known that sperm can survive several days in the woman's body and that not all eggs may be retrieved. A misdiagnosis could result if **pregnancy occurs due to a spontaneous conception.**

BENEFITS

The main benefit of PGT-M for genetic disease is increasing the chance of having a healthy child prior to initiation of a pregnancy. Since embryos without the familial genetic disease will be considered for transfer, PGT-M allows couples with a significant family history of a specific genetic disease to drastically reduce the risk of this disease in their offspring.

RISKS AND LIMITATIONS

Even though the benefit of PGT-M is considerable, there are some associated risks and limitations. PGT-M cannot guarantee a healthy pregnancy or eliminate the risk for miscarriage, stillbirth or the birth of a child with abnormalities.

Biopsy:
It is possible that a normal biopsied embryo may be slightly less likely to implant than a normal embryo that has not been biopsied. In addition, an embryo may be damaged during biopsy and it may stop developing or not be suitable for transfer. With a skilled embryologist, the risk of damaging an embryo is expected to be very low. Igenomix Canada is not responsible for any potential embryo damage. Embryo biopsy has been performed for over 20 years with thousands of babies born. Studies indicate that the risk of congenital defects is similar to the general population rate which is about 3-5%.

Cell preparation:
Once the cells are removed from the embryo, they are transferred into a small tube. It is possible that the cells are not transferred into the tube, so there is no genetic information present to test. It is also possible that the genetic material is degraded (poor quality), so it does not amplify

successfully. In either case, PGT-M results would NOT be obtained. Igenomix Canada is not responsible if a cell is not present in the tube or if the DNA is poor quality.

Transport:

A courier is used to transport the cells to Igenomix Canada for analysis. Adverse travel conditions can delay the receipt of the sample and on rare occasions can cause damage. While very unlikely, loss of the sample is also possible. Igenomix Canada is not responsible for any loss or damage to a sample related to transport.

Analysis:

The accuracy of this testing is over 98%, therefore, the misdiagnosis rate is less than 2% for the genetic disease. There are a few reasons this testing is not 100% accurate. This testing relies on the specific mutation(s) causing the familial disease to be known. If the wrong mutation(s) are evaluated, then the testing will not be accurate. It is also possible for the assay to partially fail by not identifying a mutation that is present, most frequently related to allele drop-out. The markers are included to try to eliminate this occurrence. In addition, contamination from other embryos or individuals cannot be completely ruled out and affects the accuracy of the result.

This testing only evaluates for the known genetic disease in the family. It is possible for an embryo to have a different genetic disease that was not analyzed. Also, this test does not evaluate for chromosome abnormalities such as Down syndrome. Preimplantation Genetic Testing for Aneuploidy (PGT-A) by NGS is available for testing for chromosome abnormalities. You can speak with your healthcare provider further about this additional testing. Physical birth defects such a heart defect often occur in the presence of normal chromosomes. For this reason, standard ultrasound evaluation during pregnancy is still recommended. Some conditions are multifactorial, meaning they occur due to a combination of genetic and environmental influences. Currently, testing of embryos or pregnancies is not possible for the majority of these conditions since the exact cause is not known. Examples of these conditions include autism, schizophrenia, and diabetes.

No Normal Embryos:

In some women, all the embryos are abnormal, so there is no embryo transfer.

No Diagnosis:

It is possible that a result might not be obtained from an embryo. The risk of no result is less than 2%. The most common reasons are no cells are present in the tube for testing or poor quality genetic material (common in damaged or dying cells). Some couples choose to transfer embryos without a result. The benefits associated with PGT-M would not apply to these embryos.

ALTERNATIVES

PGT-M is considered an optional test. Testing for a genetic disease can be performed during pregnancy by CVS, amniocentesis, and sometimes ultrasound examination. The risks, benefits, and limitations of testing should be discussed with you by the physician performing/ordering these tests or by a genetic counselor. PGT-M is NOT a replacement for prenatal testing.

COSTS

The fees for PGT-M are separate from the costs of the IVF cycle and embryo biopsy. This testing requires a workup which must be paid prior to the initiation of the work-up. The work-up fee is not refundable. If PGT-M is cancelled, the payment related to the work-up is non-refundable. Insurance coverage may be available for PGT-M. A detailed receipt of payment can be provided to you to submit to your insurance company for potential reimbursement. If full reimbursement is not received from your insurance company, you will not receive additional reimbursement from Igenomix Canada.

CONFIDENTIALITY

Igenomix Canada keeps test results confidential and is in compliance with all applicable Canadian laws and regulations regarding the protection of personal information, including personal health information (the "**Personal Information**"). Igenomix Canada will release your test results only

to your designated IVF physician unless otherwise directed by you (or a person legally authorized to act on your behalf) in writing, or as otherwise required by the applicable laws. Health Canada or another appropriate authority may have access to the Personal Information.

Biopsied cells will not be used for any purpose other than PGT-M. All samples are discarded within 60 days after results are reported or the test is discontinued for any reason.

I understand that by signing this consent form, I am also consenting to the storage and transfer of my Personal Information outside of Canada, specifically in Igenomix S.L. at Calle Narcis Monturiol Estarriol n. 11 Parcela B, Edificio Europark, Parque Tecnologico de Valencia, Paterna (Valencia) Spain for the DNA samples and at Azure Data Center in North Ireland the electronic files.

I understand that I have the right to access and rectify my Personal Information, or withdraw my consent at any time in respect of the collection, use and disclosure of my Personal Information, as acknowledged by the applicable Canadian laws and regulations regarding the protection of Personal Information, by writing to: **Igenomix Genetic Services Canada Inc., 200-5160 BOUL. Décarie, Montréal (Québec) H3X2H9 Canada**

I confirm that I have attained the age of majority in my province of residence. **[NTD: The age of majority is 18 in the provinces of Alberta, Ontario, Saskatchewan, Manitoba, Quebec and Prince Edward Island. The age of majority is 19 for British Columbia, New Brunswick, Nunavut, Northwest Territories, Nova Scotia, Yukon and Newfoundland and Labrador.]**

[Furthermore, I understand that my Personal Information, once anonymized, may be used for [statistical studies, evaluation, research] and I consent to such use.]

FOLLOW UP

To confirm the accuracy of the testing follow-up data is necessary. You may be contacted by someone from Igenomix Canada for pregnancy information and birth outcome. You may also donate abnormal or non-transferred embryos to Igenomix Canada for research.

RELEASE AND HOLD HARMLESS

I have had an opportunity to review and discuss this consent form and ask any questions. I understand there are benefits, risks, and limitations to PGT-M. I elect to have PGT-M for genetic disease at Igenomix Canada. I understand that PGT-M does not replace ultrasound, blood testing, CVS, or amniocentesis during pregnancy. I understand it is recommended to discuss these options further with our obstetrician or genetic counselor. I understand Igenomix Canada is solely responsible for testing the sample submitted by my healthcare provider. I understand the testing Igenomix Canada is performing cannot guarantee the birth of a healthy child; therefore, Igenomix Canada assumes no responsibility if, after testing, a child is born with abnormalities.

By signing below, I do hereby release, and hold harmless Igenomix Canada, from any and all liability, claim, loss, damage, cost or expense arising from participation in the PGT-M procedure. I hereby waive any and all claims against Igenomix Canada arising directly or indirectly, or attributable in any legal way, to any action or omission of Igenomix Canada in connection with my participation in this procedure. I hereby consent to the PGT-M procedure after being fully informed of the limitations and risks involved.

By signing below, I hereby consent to the collection, use and disclosure of my Personal Information for the purpose stated above. I understand that my Personal Information will not be disclosed to any other persons except as required to carry out the purpose stated above, as required to be disclosed under appropriate statutes, rules of law or legal process or as otherwise consented by me.

Printed Patient Name	Signature	Date
Printed Partner Name	Signature	Date