Preimplantation Genetic Testing for Aneuploidy (PGT-A) and MitoScore Consent Form - 24 Chromosome Aneuploidy

PURPOSE OF ANEUPLOIDY SCREENING BY PGT-A

Preimplantation genetic testing for aneuploidy (PGT-A), previously known as PGS, is used in conjunction with in-vitro fertilization (IVF) to screen embryos for numerical chromosomal abnormalities prior to transfer. The information obtained from PGT-A helps IVF physicians and patients decide which embryos to transfer.

Normally there are 23 pairs of chromosomes in each human cell, for a total of 46 chromosomes. Half of our chromosomes are inherited from the egg and the other half from the sperm. The appropriate number of chromosomes is necessary for normal growth and development. Extra or missing chromosomes is called aneuploidy. Aneuploidy is responsible for the vast majority of spontaneous miscarriages and can result in birth defects and mental retardation in live born babies. A common example is an extra copy of chromosome 21 (Down syndrome or trisomy 21). The chance of having aneuploid embryos increases with maternal age. PGT-A is used to identify embryos with extra or missing chromosomes. PGT-A assesses 24 chromosome types: the twenty-two autosome pairs (designated 1-22) and the two sex chromosomes X and Y. Identifying chromosomally normal embryos (euploid) prior to transfer increases the chances of achieving a successful pregnancy.

Additionally, the amount of mitochondrial DNA (mtDNA) will be assessed through the “MitoScore test”. The values obtained with MitoScore predict which euploid embryo may have a greater chance of implantation in the uterus. An increase in the amount of mtDNA in euploid embryos is correlated with a low potential of implantation and may be indicative of reduced energy reserve for oocyte maturation. Mitochondrial quantification by "MitoScore" is a value representing the normalized mtDNA content in euploid embryos and indicates the total mtDNA content in the sample (Diez Juan A, Rubio C et al. 2015).

PROCEDURE

Genetic Counseling: It is recommended that you have a consultation with a genetic counselor that specializes in PGT-A prior to signing this consent form. The genetic counselor will describe the benefits and risks of PGT-A, as well as answer any additional questions. This consultation can be arranged by calling the Igenomix Canada reference laboratory directly at 514-669-3869, or can be arranged by your IVF clinic. Please call at least 7 business days prior to your biopsy date to schedule the appointment. You may also request a consultation to review the results after the screening has been completed.

The PGT-A process is comprised of five main steps. Your fertility center will perform the first three steps including in vitro fertilization, embryo biopsy, and cell preparation steps. Then, the samples are transported to Igenomix.

In Vitro Fertilization (IVF): PGT-A requires cell(s) from embryos to be analyzed; therefore, an in vitro fertilization procedure is required. Your fertility/IVF center will advise you on this process and may require a separate consent. ICSI (intracytoplasmic sperm injection) may be performed to reduce the risk of test errors due to cell contamination. Abstinence from intercourse is recommended for two weeks prior to egg retrieval until the pregnancy test. Sperm can survive several days in a woman’s body and it is possible that not all eggs may be retrieved. A misdiagnosis could result if a spontaneous pregnancy occurs.

Biopsy, Cell Preparation, and Transport: Biopsy, cell preparation and transport procedure will take place through your IVF clinic. Igenomix can analyze biopsies from Day 3 embryos or blastocysts. Your physician will determine the type of biopsy procedure. For embryo biopsy, the embryologist at your center will remove a single cell for Day 3 biopsy (called a blastomere biopsy) or multiple cells for a blastocyst biopsy (called a trophectoderm biopsy). The embryos will remain at your IVF center. After the biopsy procedure, cell(s) are washed and transferred to a small test tube. Then the samples are transported by special courier for either same day delivery or overnight delivery (i.e. Marken, FedEx etc.) to the Igenomix laboratory. Transportation of samples is not without risks. Samples may be damaged or destroyed despite careful packaging.

Samples may also be delayed because of the weather, air travel problems or other unforeseen technical reasons beyond the control of Igenomix. On rare occasions, samples may not be received or may be damaged during transport. There is also a chance that the sample received in the Igenomix laboratory is unacceptable for analysis and results cannot be obtained. Igenomix is not responsible for any sample until it arrives at the Igenomix laboratory.

Analysis and Reporting of Results: The analysis of the cells is performed by Igenomix using advanced techniques known as array comparative genomic hybridization (aCGH), or Next Generation Sequencing (NGS). Once the analysis is completed at the Igenomix laboratory, your IVF physician will receive a report with the test results. Your physician will decide which embryos to transfer based, in part, on these results.

MitoScore: MitoScore is calculated using extracted mtDNA from the same embryo biopsy to identify those embryos that could have a greater viability and ability to lead to a pregnancy. MitoScore is analyzed using NGS and a mitochondrial marker normalized against the nuclear DNA.

BENEFITS

The majority of abnormal embryos are indistinguishable from normal embryos when studied under a microscope. Therefore, normal embryo appearance cannot be used to evaluate for chromosome abnormalities. For women in their late thirties and older, the risk for chromosome abnormalities is significantly higher than for younger women. Women with a history of recurrent miscarriage, recurrent implantation failure, a prior pregnancy with a chromosome abnormality, or men with abnormal sperm analysis may also create a higher percentage of abnormal embryos. The main benefits of PGT-A for chromosome abnormalities include an increase in implantation rate, reduction in miscarriage rate, and a higher chance of delivering a healthy baby.

Increase in implantation rate: Some embryos that are chromosomally abnormal will fail to implant into a woman's uterus. Therefore, by transferring chromosomally normal embryos, PGT-A can increase the implantation rate. Selecting the chromosomally normal embryo with the lowest MitoScore for transfer may further increase the chances of implantation.

Reduction in miscarriage rate: In the general population, 20% of all clinical pregnancies miscarry and about half are chromosomally abnormal. Since PGT-A evaluates for extra or missing copies of all chromosomes or large chromosome imbalances, embryos with chromosome abnormalities will not be transferred. Therefore, especially, in high-risk groups, PGT-A reduces the risk for miscarriage.

Higher chance of delivering a healthy baby: Some pregnancies with chromosome abnormalities will result in the birth of a child with multiple serious anomalies. Therefore, PGT-A can increase the chance of delivering a healthy baby by assisting physicians in identifying chromosomally healthy embryos for transfer. These conditions can also be detected by non-invasive prenatal test (NACE), chorionic villus sampling (CVS) or amniocentesis later during the pregnancy.

RISKS AND LIMITATIONS

1. **Risks of embryo biopsy:**
   Thus far, babies born after PGT-A or other types of procedures that include embryo biopsy have had a similar rate of birth defects to babies in the general population. Concerning embryo biopsy, there may be a risk of decreased viability of the embryo due to the biopsy procedure itself. Although data has shown that embryo biopsy has no adverse impact on growth or medical outcomes, the technique is still relatively new and the potential for unknown consequences to a live born baby cannot be excluded. However, your IVF physician has recommended PGT-A because the doctor believes that the benefits of PGT-A are likely to outweigh the risks associated with embryo biopsy.

2. **Balanced structural abnormalities:**
   PGT-A cannot detect structural abnormalities unless there is an imbalance in genetic material. There are multiple chromosomal abnormalities, including but not limited to balanced translocations and inversions that Igenomix cannot test for.

3. **Detection limit:**
   PGT-A technology is designed to test for aneuploidy (whole chromosomes that are extra or missing). It can also detect partial aneuploidy, including deletions, duplications, and unbalanced translocations, depending on the size of the chromosome segment involved. Extra or missing chromosome segments, smaller than 10 MB, usually cannot be detected.

4. **Mosaicism:**
   Mosaicism means that there are cells with differing genetic makeup present in the biopsy sample sent for genetic testing (i.e. some cells with 46 chromosomes and some with 47 chromosomes). Mosaicism occurs by chance during embryonic development and can underlie birth defects or cognitive impairment in individuals. An embryo may be reported as mosaic if it appears that there is more than one genotype in the biopsy sample. It should be noted that an embryo with a mosaic result is at increased risk of being mosaic. Furthermore, the level of mosaicism in the biopsy specimen cannot predict the level of mosaicism in the embryo as a whole. The outcome of transferring an embryo diagnosed as mosaic cannot be predicted. A mosaic embryo may not implant, may miscarry spontaneously, may develop abnormally, may result in the birth of a child with mild to severe birth defects and mental retardation, or may result in the birth of a healthy child. Due to this uncertainty, Igenomix does not recommend the transfer of embryos diagnosed as mosaic. You should discuss with your physician and/or a genetic counselor if you wish to transfer an embryo diagnosed as mosaic.

   PGT-A is performed on the biopsy of an embryo; the embryo as a whole cannot be tested. The possibility of mosaicism cannot be excluded. An embryo diagnosed as normal may still contain mosaicism. Mosaicism may lead to a misdiagnosis by PGT-A. See “Misdiagnosis by Chromosomal Mosaicism” below.

   A mosaic results indicates the presence of more than one genotype within the biopsy. At this time, Igenomix reports samples as mosaic when it is determined that more than 30% and less than 75% of the cells in the biopsy are aneuploid, based on our own internal validation of PGT-A testing by NGS.

5. **Other birth defects or genetic/developmental anomalies not tested during PGT-A:**
   Birth defects: PGT-A cannot detect all potential birth defects. There is a 3-5% risk in the general population for birth defects. These may be caused by genetic and/or non-genetic etiologies.

   Single gene mutations: PGT-A for aneuploidy does not analyze specific genes and cannot detect conditions caused by single gene mutations, such as sickle cell anemia, cystic fibrosis, or Tay-Sachs disease. Any known genetic conditions in the family should be discussed with your fertility doctor.

   Uniparental disomy (UPD): UPD is the presence of two copies of a given chromosome from one parent and none from the other. UPD for certain chromosomes is associated with particular genetic syndromes or medical, cognitive or physical disabilities. Igenomix is unable detect UPD via PGT-A.

   Polyploidy: PGT-A cannot detect polyploidy, in which there is a numerical change in a whole set of chromosomes. Polyploidy may arise from fertilization of an egg by more than one sperm (polyspermy), fertilization of a diploid egg, or fertilization by a diploid sperm.

6. **Misdiagnosis:**
   Misdiagnosis due to test error: PGT-A testing cannot be 100% precise or exact. There remains an empirically determined 1-2% chance of a misdiagnosis, either by a false negative or a false positive result. A false negative result indicates an

embryo has a normal number of chromosomes when in fact, it contains a chromosomal abnormality. A false positive result indicates an embryo is aneuploid when it is chromosomally normal.

Misdiagnosis due to mosaicism: Mosaicism can cause a misdiagnosis if the cells that are tested are not representative of the embryo. PGT-A cannot rule out mosaicism because only one cell or a few cells are biopsied and analyzed.

7. **No diagnosis:**
   Transportation problems may occur, such as weather and air travel delays, or other circumstances beyond the control of Igenomix that would not allow results to be obtained in a timely manner for embryo transfer. Samples received in the Igenomix laboratory may be unsuitable for analysis and results may not be obtained from the sample provided. On rare occasions, genetic testing cannot be performed due to improper biopsy techniques, loss of biopsied cells, or poor DNA quality (often found in damaged or dying cells).

8. **Inconclusive results:**
   A statistical model is used to determine the number of chromosomes for each embryo sample. In some cases, due to degraded DNA or other unusual characteristics in a sample, the data will not conform to the statistical model. These results will be reported as inconclusive.

9. **No normal embryos:**
   It is possible that all embryo samples tested during an IVF cycle will be found to have aneuploidy and no embryos will be suitable for transfer. Likewise, an embryo sample may be found to be chromosomally normal but the embryo may not develop normally and will not be selected for transfer.

10. **Intracytoplasmic Sperm Injection (ICSI):**
    ICSI as a method of fertilization is recommended, but not required prior to PGT-A. If ICSI is not performed, there is an increased risk of "no results" on one or more samples due to contamination of the sperm.

11. **MitoScore:**
    This test provides information about the chance of implantation of each embryo, with low values indicating better implantation capacity. High values indicate lower implantation potential, but do not suggest abnormalities in the embryo. The MitoScore does not provide information about the health of a pregnancy and all embryos remain candidates for transfer, regardless of the MitoScore value. Your physician may choose to employ the grading system based on an evaluation of the appearance of the embryo rather than the MitoScore test to determine which chromosomally normal embryo is the best candidate for transfer. Selecting embryos based on their morphological grade is the traditional method employed by embryologists.

ALTERNATIVES

The risks, benefits and alternatives of PGT-A testing should be discussed thoroughly with your genetic counselor, obstetrician or the person performing/ordering the tests. PGT-A for aneuploidy is an optional test that is offered to increase the chance of having a healthy live born baby. You are not obliged to undergo PGT-A even if your physician recommends it. Proceeding with an IVF cycle without PGT-A is an alternative option. Prenatal screening, prenatal diagnosis, and ultrasound examination are available to evaluate chromosomal abnormalities and/or birth defects.

RECOMMENDED FOLLOW-UP TESTING

PGT-A cannot guarantee the birth of a chromosomally normal child. Due to the chance of misdiagnosis, the inability to rule out mosaicism and structural abnormalities, and the screening nature of PGT-A, prenatal diagnosis for ongoing pregnancies

is recommended to confirm the PGT-A results. PGT-A should not be considered a replacement for prenatal testing. A prenatal genetic counselor can discuss which type of prenatal testing may be most appropriate for you. If a pregnancy loss occurs, we recommend that chromosome studies be performed on the products of conception.

COSTS

Fees for PGT-A are in addition to any other costs associated with the IVF cycle. Fees must be either paid to Igenomix directly or paid to your IVF center (depending on the payment protocol at your IVF center). All fees paid to Igenomix are due prior to biopsy screening. Your IVF center finance department or an Igenomix financial coordinator will advise you of the fees. If the PGT-A procedure is paid for but not performed (for any reason including cancellation, lack of suitable embryos for biopsy, or transportation delay), your payment will be refunded.

CONFIDENTIALITY AND DONATION FOR RESEARCH OR DISPOSAL OF SAMPLES

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 law. Health Canada or another appropriate authority may have access to the Personal Information. Identity will be concealed, but PGT-A results may be included in medical publications without an additional consent.

DNA extracted from biopsy cells will be used for PGT-A and MitoScore. Surplus DNA can be discarded within 60 days after results are reported or if the test is discontinued for any reason; it is also possible to donate the surplus DNA samples for research purposes.

The goal of sample donation is to find answers and solutions related to infertility and help infertile couples become pregnant. If you agree, these samples may be used to further examine and develop new technologies and/or other research in the area of In Vitro Fertilization, embryo genetic testing and carrier screening. Donated materials will never be used to make new embryos or future babies.

Donated samples will be de-identified, and the material transfer will not include any of your protected health information. The researchers studying the donated materials will not know your identity, and all identifiers associated with the donated materials will be removed prior to their release for research. Data generated from the research studies may be published without any identifying information and may be shared with multiple researchers within and outside of Igenomix Canada including commercial entities.

This donation involves no additional immediate, direct medical risk to you. The future research is not intended to provide direct medical benefit to you or anyone else.

Any material you have donated to research, or results of research including new products, tests, or discoveries, may be patentable or have commercial value. If you consent to donate materials, you will have no legal or financial interest in any commercial development resulting from the research.

Your decision to participate in research studies with your donated samples is voluntary. You have the right to withdraw your consent at any time prior to the release of your cellular reproductive materials to researchers. If you decide not to be a donator, sample will be discarded after PGT-A /MitoScore tests. However, once the materials are provided to researchers, you will not be able to withdraw them from the research. To withdraw, please contact Igenomix Canada. Neither consenting

nor declining to donate materials for research will affect the quality of care provided to you by this facility. Clinical decisions about your IVF treatment will not be influenced by your participation. The researchers will not be involved in your direct clinical care. **Please check the boxes that apply to you and sign below:**

☐ I wish to donate samples from extra DNA for research: Patient Initials:_____ Partner Initials:_____

☐ I wish the samples to be discarded after PGT-A /MitoScore tests: Patient Initials:_____ Partner Initials:_____

☐ *Optional:* Check this box if you do not object to being contacted in the future to be offered the opportunity to conduct research or complete medical information about your case. Failure to check this box does not involve any commitment on your part to accept participating in the study.

CONSENT FOR PGT-A/MITOSCORE

I have read this Patient Consent Form completely and have decided to proceed with PGT-A/MitoScore test for aneuploidy and transfer selecting embryos. I request that Igenomix Canada perform PGT-A/MitoScore on all embryo samples sent by my IVF doctor and 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 unless required to be disclosed under appropriate statutes, rules of law or legal process or as otherwise consented by me. This consent applies to this and all future IVF cycles in which embryo testing with Igenomix Canada is requested.

I understand that by signing this consent form, I/we am/are also consenting to the storage and transfer of my Personal Information outside of Canada, specifically, in Igenomix USA at 7955 NW 12th Street Suite 415, Miami FL 33126 USA for the DNA samples and in 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 to 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.]

I acknowledge that PGT-A/MitoScore has both benefits and risks, some of which may as yet be unknown.

I acknowledge that PGT-A can determine whether a chromosomal abnormality could affect the embryo. However, I understand that PGT-A cannot detect all chromosomal abnormalities and that my/our pregnancy must be followed by our IVF physician, obstetrician, and/or other appropriately trained healthcare professional. Igenomix Canada encourages prenatal diagnosis (CVS or amniocentesis) during the resulting pregnancy to confirm the results of PGT-A. I understand that standard prenatal testing is recommended whether PGT-A for aneuploidy is performed or not. I understand that if I have questions about prenatal testing I may ask a genetic counselor or obstetrician.

I acknowledge that Igenomix Canada is committed to monitoring the outcome of PGT-A and understand that Igenomix Canada may contact me to inquire about the outcome of my IVF cycle. I acknowledge that I may be contacted throughout

the course of the pregnancy and afterwards about the pregnancy outcome and to follow up on the health of the child. Any information received during these follow-up encounters shall remain strictly confidential. Information received will not be used for any purpose other than to advance the science of genetic testing of preimplantation embryos and will be de-identified (anonymous) for any public use.

I have been given the opportunity to talk with an Igenomix Canada genetic counselor by telephone to ask questions about PGT-A and MitoScore and the information contained in this consent form. I understand that the Igenomix Canada genetic counselor is available to answer any additional questions. If I decide to complete this form prior to speaking with the genetic counselor, I acknowledge that I will be able to ask any questions that I may have with the genetic counselor during a future appointment. I acknowledge that the request for genetic counseling must occur at least three business days before the biopsy date. If I decide to do testing within three days of the biopsy date, I agree to have testing performed without first speaking to the Igenomix Canada genetic counselor and to pay all associated testing fees.

I acknowledge that Igenomix Canada may not be held liable in any manner whatsoever for any birth defects, chromosomal abnormalities, false positive findings, false negative findings, shipping or transport errors or omissions, nor for any damage in contract or tort arising out of Igenomix PGT-A screening.

I acknowledge that any legal controversy, dispute, or disagreement arising out of the services provided by Igenomix Canada or any subsidiary thereof shall be referred to and finally resolved by arbitration under the Canadian Arbitration Association Arbitration Rules. The place of the arbitration shall be Montreal. This agreement is governed by the laws of the province of Quebec and the laws of Canada applicable therein.

Choose the type of test requested:

- ☐ PGT-A
- ☐ PGT-A + MitoScore

By signing this Patient Consent Form you are: (i) agreeing to arbitration as set forth above, and (ii) acknowledging that you have been advised to and have had the opportunity to consult with independent counsel concerning this arbitration.

My signature below means that I have read and understand this Patient Consent Form. I have been encouraged to ask questions about any portion of this Igenomix Canada Patient Consent Form and to consult with family, friends and/or medical or legal advisors as I see fit. This Patient Consent Form is the only agreement between Igenomix Canada and me to provide PGT-A. I explicitly acknowledge that this Patient Consent Form obligates me to participate in arbitration should any dispute arise out of this agreement. I consent to PGT-A for aneuploidy by Igenomix Canada.

Signature of Patient	*Printed Name*	*Date*
Signature of Partner	*Printed Name*	*Date*