INFORMED CONSENT FOR PREIMPLANTATION GENETIC TESTING FOR MONOGENIC DISEASES (PGT-M)

DESCRIPTION, PURPOSE AND ADVANTAGES OF PERFORMING THE ANALYSIS

Preimplantation Genetic Testing for Monogenic Diseases (PGT-M) is used to analyse embryos for a specific genetic disorder before transfer.

Almost every cell in our body has chromosomes, which are organised structures made up of DNA and proteins. There are 24 different types of chromosomes in humans, numbered from 1 to 22, plus the sex chromosomes X and Y. Most human cells contain a total of 46 chromosomes: 22 pairs, an XX pair for a biological female and an XY pair for a biological male. Both the sperm and the egg must have 23 chromosomes. Therefore, when a sperm fertilises an egg, the resulting embryo has 46 chromosomes in total.

Chromosomes are made up of molecules called DNA. Our DNA is arranged into small fragments called genes. There are around 20,000 genes in humans, all of which have an influence on our growth and development. As with chromosomes, the majority of genes exist in pairs, one inherited from the egg and the other from the sperm. When the function of a gene is altered by a change (mutation) in the specific sequence, the result might lead to a genetic disease. These mutations can be transmitted from generation to generation or they can occur for the first time in the individual (de novo).

Genetic diseases may be caused by different modes of inheritance for a mutation:

I. A dominant genetic disease is caused by a mutation in one copy of a gene. There is a 50% risk that a parent with the disease will pass it on to their children.
II. A recessive genetic disease is caused by the presence of a mutation in both copies of a gene. An individual who has one normal copy of the gene and one mutated copy is considered to be a carrier. The majority of carriers are healthy, as having a normal copy is usually enough to prevent the disease. If both parents are carriers for the same condition, they have a 25% risk of having a child with the genetic disease.
III. Genetic diseases associated with biological sex are normally caused by mutations in the X chromosome. The majority of these sex-linked diseases are recessive and mainly affect biological males and in certain occasions and to a lesser extent biological females; however, some may be dominant and will affect both biological males and biological females in a different way.

The main benefit of performing PGT-M is to increase the chance of having a healthy baby given that the analysed embryos found to be free from the genetic mutation will be considered for transfer. This allows couples who are undertaking PGT-M to considerably reduce the risk of transmitting the specific disorder to their future children.

PROCEDURE, RISKS AND LIMITATIONS

There are several stages in the PGT-M process. The first three steps are carried out at your IVF clinic: in vitro fertilization (IVF), embryo biopsy and cell preparation. The cells collected in the embryo biopsy are then transferred to Igenomix for subsequent analysis.

In vitro fertilization (IVF):

PGT-M analyses cells taken (i.e., biopsied) from an embryo. Therefore, an IVF cycle is required regardless of your fertility history. Your IVF clinic will advise you on this process and may require additional consent. An ICSI (intracytoplasmic sperm injection) is recommended to reduce the risk of errors in the test due to contamination. Abstaining from sexual relations for at least two weeks before egg collection and for the time leading up to the pregnancy test is also recommended. We know that sperm can survive several days in the body of a female and that not all the eggs are removed during the collection process in the IVF cycle. A spontaneous pregnancy may give an incorrect diagnosis.

Embryo biopsy, cell preparation and transport:

The embryo biopsy is carried out on day 5-7 of embryonic development when the embryo is at the blastocyst stage (trophectoderm biopsy). In the trophectoderm biopsy, several cells are removed from each blastocyst for PGT-M analysis. After the biopsy, the embryos will remain at the IVF clinic and will be frozen by a process known as vitrification.

After performing the biopsy, the cells obtained are "cleaned" by the embryologist to eliminate any potential source of contamination and are then transferred to a small tube supplied by Igenomix.

These tubes containing the cells are then safely packaged into an Igenomix cooler and sent by courier to the laboratory. Depending on the location of the IVF clinic, the samples will take 1-7 days in transit to arrive to the laboratory.

Analysis:

Once the laboratory receives the biopsy samples, the genetic material is amplified to make it suitable for downstream processes. The PGT-M test will use the same testing strategy developed in your pre-PGT-M test that includes the evaluation of genetic markers to determine "phase" and, whenever required, the detection of the mutation(s) that causes the disease. The markers are regions with variable sequences which are within or closely linked to the gene in the study. Embryos out of "phase" and not inheriting the mutations are considered normal and recommended for transfer. If PGT-M is being conducted for a recessive disease and one parental phase and/or mutation is identified, the embryo is classified as a carrier and is also considered for transfer.

To process the sample, the test requisition form will need to be correctly completed. If this is not the case, the analysis may be suspended until the information required has been provided to the laboratory.

Given the complexity of the genetic tests and the significant implications of the test results, the results obtained must be interpreted in conjunction with other clinical data, within the general context of a medical practice run by healthcare professionals. The result reports are strictly confidential.

The results of the test will be available within 10 working days of receipt at the samples at the laboratory. A small percentage of samples may be delayed due to unforeseeable causes. Should this occur, your IVF clinic/doctor will be notified.

PGT-M does not entirely eliminate the risk of offspring developing the disorder, cannot guarantee a healthy pregnancy or eliminate the risk of miscarriage, death or the birth of a child with abnormalities. The main risks and limitations associated with PGT-M are:

1. **Risks due to biopsy:**

It is possible that the implantation capacity of a normal biopsied embryo is slightly reduced compared to a normal embryo which has not been biopsied.

It is possible that the embryo may become damaged during the biopsy and will stop developing or not be suitable for transfer. However, when handled by skilled embryologists, the risk of damage to the embryo is very low. Igenomix is not responsible for any potential damage to the embryo.

2. **Risks due to cell preparation:**

Once the cells are removed from the embryo, they are transferred to a small tube. Occasionally, the cells may not be successfully transferred to the tube, in which case there would be no cellular material to perform genetic analysis on. It is also possible that the genetic material is degraded (poor quality), in which case it would not be successfully amplified. In either of these cases, results from PGT-M will not be obtained for the embryo. Igenomix is not responsible in the event that a cell(s) is not present in the tube or if the DNA is of poor quality.

3. **Risks due to transport:**

The cells are sent via courier to Igenomix for analysis. Certain adverse conditions during transportation may cause a delay in receiving the sample or, on rare occasions, cause damage to the sample(s). Although highly unlikely, a sample(s) could also be lost. Igenomix is not responsible for any loss or damage to a sample during transport.

4. **Risks due to the analysis:**

The accuracy of this test is over 98%, therefore, the misdiagnosis rate is less than 2% for the genetic disease. There are a number of factors that prevent PGT-M from being 100% accurate:

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i. The test relies on a "genetic report" (obtained prior to PGT-M) that describes the specific mutation(s) causing the disease. Errors in the "genetic report" (e.g. incorrect mutation) will compromise the accuracy of PGT-M.
ii. Contamination from other embryos or individuals involved in the IVF/PGT-M process may reduce the accuracy of the test.
iii. Allele drop-out, a phenomenon resulting from testing a small number of single cells and that affects the amplification of the genetic region of interest may reduce the accuracy of the test
iv. The presence of "recombination" in the embryos that cannot be detected at the pre-PGT-M stage may affect the accuracy of the test

PGT-M will only test for the known genetic disease in the family described in the "genetic report(s)". It is possible for an embryo to have a different genetic disease or mutation not specified in the "genetic report(s)" that will not be analysed. Furthermore, PGT-M performed with Karyomapping will detect certain chromosomal abnormalities (aneuploidies) that will be included in the report and that will influence the recommendation for transfer of an embryo.

Karyomapping is currently accredited for the detection of certain aneuploidies known as "meiotic" aneuploidies. Meiotic aneuploidies detected by Karyomapping are highly likely to be present in the majority of cells of the embryo and will contribute to failed implantation, miscarriage or even the birth of a child with a genetic disorder associated with these aneuploidies. There are other kinds of aneuploidies known as mitotic or mosaic aneuploidies that might be detected by Karyomapping and that will be mentioned in the "comments" section of the report. .

Physical birth defects such a heart defects 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 both genetic and environmental factors. Currently, testing of embryos or pregnancies is not possible for the majority of these conditions since the exact cause(s) is not known. Examples of these conditions include schizophrenia and diabetes. The embryo biopsy and all the laboratory procedures are carried out in sterile conditions to avoid contamination with genetic material which does not come from the embryo and that may obscure the results.

5. No diagnosis:

It is possible that no result is obtained from an embryo. The risk of obtaining no result whatsoever is less than 5%. The most common reasons are the absence of cells in the test tube or poor-quality genetic material (common in damaged or dead cells). Some patients choose to transfer embryos despite a "no result". The benefits associated with PGT-M would not be applicable to these embryos.

6. No normal embryos:

For some patients it could happen that all the embryos are diagnosed as abnormal. Therefore, no embryo is transferred.

7. ICSI:

The recommended laboratory technique for the fertilization of eggs is ICSI. If ICSI is not performed, the risk of an incorrect result increases due to the contamination of the sample with DNA from sperm or from maternal granulosa cells that adhere to the external surface of the embryo.

DATA PRIVACY, STORAGE AND RESEARCH USE OF SAMPLES

Your privacy is a priority for the Igenomix Group ("Igenomix"). Your identity and all data referring to your personal information will be confidential and only Igenomix personnel will be permitted access to this information, along with the relevant authorities when required by the laws of the applicable jurisdiction. You will find further information on the Igenomix Privacy Policy, along with all your rights at www.igenomix.com, or this information may be provided to you upon request by sending an email to privacy@igenomix.com.

We would like to inform you that your personal data will only be processed to: (1) Fulfil the obligations arising from the provision of the services contracted by you; (2) Check and guarantee the quality of the services provided (internal audits, quality controls, laboratory validation studies); (3) For educational purposes, provided that it remains anonymous throughout and you cannot be identified during the analysis of the data, which will not be linked to your personal data; (4) For research purposes, scientific publications and presentations, provided that it remains anonymous throughout and you cannot be identified during the analysis of the data, which will not be linked to your personal data; and (5) Personally address any doubts or suggestions made by the patient during the process and monitor the proper performance and resolution of the test, including the indefinite retention of your data, except where local laws of the applicable jurisdiction state otherwise.

You also declare that you understand and accept that you will not obtain, either now or in the future, any economic benefit for any research carried out, and that there is no intention to compensate you for the products developed from any research.

The sample will be analysed by Igenomix or an associated group selected by Igenomix on an international level. Igenomix reserves the right to carry out part or all of the analyses included in the test through third party laboratories accredited to recognised international quality standards, or failing this, they will be periodically assessed by Igenomix. Any results obtained in this way will be inspected by Igenomix and this circumstance will be indicated in the final report issued.

The samples and data associated with the same shall be held by the laboratory in accordance with Igenomix's sample retention policy which meets all legal requirements.

Pursuant to the laws on the Protection of Personal Data[1], the requesting party must have the patient's consent to perform the diagnostic tests requested and to process their data. You may, at any time, exercise your rights regarding access, rectification, opposition, erasure, automated decisions, limitation, portability, by sending an email to privacy@igenomix.com, providing proof of the requesting party's identity.

[1]**For patients residing outside of the United States:** under certain jurisdictions, clients residing outside the United States may at any time request to have their personal information deleted from our active databases, subject to the applicable laws and regulations in each jurisdiction. Although we can delete your personal information from our active databases, part or all of your personal information shall remain stored in back-up files for the purpose of complying with legal, regulatory or other requirements. Information that has already been coded and/or anonymised may not be recoverable or traceable for destruction, deletion or modification. If you wish to have your personal information removed from our active databases, please contact us at privacy@igenomix.com.

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HAVING READ AND UNDERSTOOD THE FOREGOING, I AM AWARE OF:

The indications, procedure, success rate, risks and complications of the proposed treatment, as well as the financial cost of said test(s).

The fact that medical staff are at my disposal to expand on any aspect of the information that is not sufficiently clear to me.

I have understood the explanations given to me in clear and simple language, and the clinician who saw me allowed me to make comments, clarifying any issues I raised and informing me that I may freely withdraw my consent at any time.

I am satisfied with the information received and I freely give my consent to the taking of blood, buccal cell or saliva sample in the assisted reproduction Centre/Clinic which I have attended. I also consent to the sample being sent to Igenomix facilities alongside my embryo biopsy samples for the purpose of carrying out the aforementioned test(s).

I also accept that the results of the test(s) will be passed on to my clinician and the relevant healthcare professionals at the IVF clinic, so that they can counsel me accordingly.

Patient consent
By signing this requisition form, I voluntarily request Igenomix to carry out the test indicated above. I have read and received a copy of the informed consent, included in the previous pages. The risks, benefits and limitations of this test have been explained to me. Patient's full name and signature _____ Date_____ /_____/_____ Patient's date of birth _____/_____/_____
Partner consent (when applicable)
By signing this requisition form, I voluntarily request Igenomix to carry out the test indicated above. I have read and received a copy of the informed consent, included in the previous pages. The risks, benefits and limitations of this test have been explained to me. Partner's full name and signature _____ Date_____ /_____/_____ Partner's date of birth _____ /_____ /_____

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