INFORMED CONSENT FOR PREIMPLANTATION GENETIC TESTING FOR ANEUPLOIDIES (PGT-A), FOR CARRIERS OF STRUCTURAL REARRANGEMENTS (PGT-SR) AND FOR MITOSCORE

DESCRIPTION, PURPOSE AND ADVANTAGES OF PERFORMING THE ANALYSIS

Preimplantation Genetic Testing for Aneuploidies (PGT-A) is used in combination with in vitro fertilisation (IVF) treatment to detect chromosomal abnormalities in embryos before their transfer. Chromosomal abnormalities are often seen in embryos and frequently result in abnormal pregnancies, miscarriages and failed implantation. The information obtained from PGT-A helps clinicians and patients decide which embryos to transfer in IVF treatment.

Every cell in the body has chromosomes, which are organized structures containing DNA and proteins. This information contained within the chromosomes is necessary for growth and development. 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 and an XX pair for a female, and an XY pair for a male. Both the sperm and the egg must have 23 chromosomes to produce an embryo with the correct number of chromosomes, meaning that, when a sperm fertilizes an egg, the resulting embryo has 46 chromosomes in total.

Any female can produce chromosomally abnormal eggs and any male chromosomally abnormal sperm. If an egg with 24 chromosomes is fertilized by a sperm with 23 chromosomes, the resulting embryo has 47 chromosomes (one extra). A common example of a chromosomal abnormality is Down's syndrome, which is caused by the presence of three copies instead of two of chromosome 21. Embryo aneuploidy (extra or missing chromosomes) may develop as a result of an abnormal egg (risk groups include women over the age of 38), an abnormal sperm (severe male factor), individuals with balanced structural rearrangements (translocations and inversions), or due to a subsequent error during cell division. Chromosomal abnormalities can give rise to reproductive failure or prevent assisted reproductive treatment from resulting in pregnancy. They can also be responsible for miscarriages in the first trimester, foetal death, or newborns with chromosomal abnormalities.

Most abnormal embryos are not distinguishable from normal embryos when assessed using a microscope in the IVF clinic. Therefore, assessment of embryo morphology cannot be used to detect the presence of chromosomal abnormalities.

PGT-A detects extra or missing copies of the 24 chromosomes or large chromosomal imbalances, and embryos with chromosomal abnormalities will not be recommended for transfer. The main benefits of PGT-A include the reduction of the risk of miscarriages, the increase in implantation rate and the increase in the probability of having a healthy baby. Not all pregnancies with chromosomal abnormalities lead to implantation failure or miscarriage; some of these chromosomal alterations can result in the birth of a baby with serious abnormalities. These conditions can be detected during the pregnancy via other types of invasive tests such as chorionic villus biopsy and amniocentesis. However, these procedures involve a risk of miscarriage and cannot be performed until after the pregnancy is achieved.

In addition, the MitoScore test can be performed, which measures the mitochondrial DNA. The results obtained from this test allow us to identify which of the chromosomally normal (euploid) embryos of a patient might have a greater chance of implantation. An increase in the mitochondrial DNA (mtDNA) in euploid embryos was shown in some studies to be associated with a lower implantation potential and can be indicative of a reduced energetic capability during the maturation of oocytes. MitoScore is a value which shows the standard amount of mtDNA in euploid embryos and indicates the total amount of mtDNA in the sample (Diez-Juan A, Rubio C et al. 2015).

Selecting chromosomally normal embryos with a lower MitoScore value can further increase the likelihood of implantation.

PROCEDURES, RISKS AND LIMITATIONS

The PGT-A process consists of several phases. The first three phases are carried out at your IVF clinic: the in vitro fertilization, embryo biopsy and cell preparation. The biopsied cells are then transferred to Igenomix for subsequent analysis.

In vitro fertilization (IVF):

A PGT-A cycle needs an embryo cell or cells to analyse. Therefore, an IVF cycle is required regardless of fertility history. Your IVF clinic will advise you on this process and may require additional consent. An Intracytoplasmic Sperm Injection (ICSI) is recommended. It is also recommended to abstain from sexual intercourse for at least two weeks before the removal of the eggs and for the time leading up to the pregnancy test. Sperm can survive several days in the body of a female and not all of the eggs are removed during the egg retrieval process in the IVF cycle. A spontaneous pregnancy may lead to an incorrect diagnosis.

Embryo biopsy, cell preparation and transport:

The embryo biopsy can be carried out on day 5, 6 or 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-A. After the biopsy, the embryos will remain at the IVF clinic. Depending on the stage of the cycle and your clinician's recommendation, the embryos could be frozen after the biopsy and before the results are received. This process is known as vitrification of embryos.

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

These tubes containing the cells are then sent by courier to the laboratory, always under the strict temperature control and security conditions required by Igenomix. Depending on the location of the IVF clinic, the samples will arrive on the same or following day.

Analysis and reporting of the results:

Once the laboratory receives the samples, the genetic content (DNA) of the cells is amplified to increase the amount of genetic material present for evaluation. This sample is then prepared and analysed using Next Generation Sequencing. If the sample contains excess or

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missing genetic material for one chromosome (i.e. an aneuploidy in one chromosome), the embryo is classified as "abnormal" ; if aneuploidy is detected in 2-5 chromosomes, the embryo is classified as "complex abnormal"; embryos with aneuploidies in more than 5 chromosomes are classified as "chaotic abnormal". Abnormal embryos of any kind are NOT recommended for transfer. The results are sent directly to the IVF clinic and your clinician will indicate which embryo(s) to transfer based on this information.

MitoScore:

The MitoScore test can also be performed on the DNA obtained from the same biopsy to identify which embryos could have a greater capacity and suitability for achieving pregnancy. The level of mitochondrial DNA (MitoScore) is obtained using NGS, which offers information on both the nuclear and mitochondrial DNA.

To process the sample, the test request form will need to be correctly filled out. 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 test result will be available: within 24 hours for a transfer during the same cycle, provided that the samples are received at Igenomix first thing in the morning on the day following the biopsy; within 10 working days following receipt of the sample at Igenomix for a deferred cycle. A small percentage of samples may be delayed due to unforeseeable causes. Should this occur, your clinic will be notified.

PGT-A does not eliminate the risk of an offspring developing a disorder and it 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-A and MitoScore 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. However, there is evidence to suggest that the preferential selection of chromosomally normal embryos more than offsets any potential adverse effects of the biopsy and in general, the implantation rate will be greater if the technique allows for the analysis of all the chromosomes.

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. **Preparation of cells:**

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

3. **Transport:**

The cells are sent via courier to Igenomix for analysis. Any unexpected events during transport may delay reception of the sample and on rare occasions, cause damage to them. It is also possible, however unlikely, that the sample may be lost. Igenomix is not responsible for any loss or damage to a sample during transport.

4. **Limits in detection:**

PGT-A is a test designed to detect aneuploidies (losses or gains of whole chromosomes) and it can also detect partial aneuploidies, including deletions, duplications and unbalanced structural rearrangements, depending on the segment size of the affected chromosome. PGT-A does not allow us to detect gains or losses in chromosome segments smaller than 10 Mb (Megabases). These abnormalities are rare unless there is a family history of them.

5. **Test limitations of PGT-A**

Accuracy: The accuracy of this test is higher than 98%. The risk of birth defects is between 3 and 5% in the general population and may be due to other genetic or non-genetic causes, which are not necessarily due to alterations in the number of chromosomes.

Balanced structural rearrangements: PGT-A does not allow us to detect balanced structural rearrangements (such as balanced translocations and inversions). In other words, abnormalities in the structure of the chromosomes which do not result in gains or losses in chromosomal material will not be detected by PGT-A.

Genetic mutations: Not all genetic abnormalities are due to chromosomal abnormalities. For example, to detect the presence of alterations in individual genes, such as cystic fibrosis, sickle cell anaemia or haemophilia, tests must be performed to detect the particular change in the familial gene (mutation). Any known familial genetic alteration should be discussed with your clinician.

Uniparental disomy (UPD): This is the presence of two copies of a chromosome from one partner, which is associated with genetic syndromes with clinical manifestation or cognitive deficits, related to the chromosome in which the UPD presents. Igenomix cannot detect UPD using PGT-A.

Ploidy: PGT-A cannot detect haploidy, triploidy or tetraploidy, which are alterations of the entire set of chromosomes, with the presence of one, three or four copies of each and every one of the chromosomes contained in a cell respectively. These types of chromosomal

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alterations, which we would not be able to identify, would lead to miscarriages and partial molar pregnancies, but their incidence in human preimplantation embryos is less than 1%.

In addition, physical birth defects may appear, such as heart alterations, which are not related to chromosomal alterations. Some illnesses are multifactorial, which means that they occur due to a combination of genetic and environmental influences. Currently, studies on embryos or on foetuses during pregnancy are not possible for the majority of these conditions as the exact cause is unknown. Some examples of these conditions are autism, schizophrenia and diabetes.

For these reasons, ultrasound monitoring is recommended if pregnancy is achieved.

6. Mosaicism:

Mosaicism is defined as the presence of more than one type of chromosomally different cell in an embryo. A mosaic embryo contains a combination of chromosomally normal cells and cells with aneuploidies. Mosaicism occurs randomly and spontaneously during embryonic development. During the process of cell division, the chromosomes may not be distributed equally, giving rise to cells with an abnormal number of chromosomes. An embryo will be considered mosaic when the level of aneuploidies detected in the biopsy is between 30% and 70%, based on our internal validation of PGT-A using NGS. Embryos will be considered to have "low-level mosaicism" if the level of aneuploidy in the biopsy is between 30% and 50%; and "high-level mosaicism" if the level of aneuploidy in the biopsy is between 50% and 70%. Embryos with aneuploidy levels above 70% will be reported as "abnormal" (aneuploid), and embryos with aneuploidy levels below 30% will be reported as "normal" (euploid). Mosaicism is not reported when the aneuploidy involves chromosomes 13, 18, 21, X or Y; embryos with an aneuploidy level greater than 30% in any of chromosomes 13, 18, 21, X or Y will be reported as "abnormal". Embryos that have another uniform aneuploid chromosome will never be reported as mosaic, but as abnormal.

There is limited clinical information regarding the reproductive result of mosaic embryos. The most recent data indicate that mosaic embryos have a lower potential for implantation, final development and healthy birth compared to chromosomally normal embryos. However, mosaic embryos may have a greater potential to lead to a healthy pregnancy compared to embryos that are diagnosed as entirely aneuploid (i.e. abnormal).

The decision on which embryos to transfer is made by the patient and the clinician. The patient must talk to their clinician if they wish for a mosaic embryo to be transferred. The level of mosaicism detected in biopsied cells may not be representative of the whole embryo; an embryo with "high" or "low" level mosaicism has a greater risk of developing some type of abnormality. Embryos with low levels of mosaicism may be more likely to result in healthy babies than embryos with high levels of mosaicism. In addition, it should also be taken into account that an embryo diagnosed as mosaic has a high risk of being mosaic throughout, but it remains possible that the inner section of the embryo (the inner cell mass), which will develop into the foetus, is made up of chromosomally normal cells. Chromosomally normal embryos are more likely to result in a successful pregnancy than mosaic embryos and should be prioritised accordingly.

A "normal" result suggests that no mosaicism was detected in the biopsied sample, or any aneuploidy that was detected was at a level below 30%; the PGT-A test cannot rule out the presence of mosaicism in the whole embryo. An embryo diagnosed as normal may have chromosomal abnormalities in other cells that were not biopsied, which may lead to a diagnostic error.

7. Error in diagnosis:

PGT-A has a 1 to 2% chance of error. One possibility is a 'false positive'. This means that normal embryos are diagnosed as abnormal. Conversely, there is the possibility of a 'false negative', meaning that abnormal embryos are diagnosed as normal. False negatives may be due to the presence of mosaicism, as explained above, with the biopsy analysed not always being representative of the whole embryo.

The embryo biopsy and all the laboratory procedures are carried out under sterile conditions to avoid contamination or the presence of genetic material which does not come from the embryo and may lead to incorrect results.

8. No diagnosis due to the absence of DNA:

It may not be possible to obtain results from an embryo biopsy. The likelihood of not getting results is less than 4%. The most common reasons for this are the absence of cells in the test tube or poor-quality genetic material (common in cells damaged during the biopsy process). Some couples choose to transfer embryos with a result of "No DNA detected". When transferring embryos without a diagnosis, the benefits associated with the PGT-A do not apply.

9. Non-informative results:

When the quality of the sample is insufficient, the statistical model used to determine the number of chromosomes does not allow for a conclusive result. In this case the diagnosis will appear on the report as non-informative. Some couples choose to transfer embryos with a non-informative result. When transferring these embryos, the benefits associated with the PGT-A do not apply.

10. Absence of embryos for transfer:

In some women, all the embryos are diagnosed as abnormal, and no embryo is recommended for transfer.

11. ICSI:

The recommended laboratory technique for the fertilization of eggs to undergo PGT is ICSI, but this is not required by some IVF clinics. If ICSI is not performed, the risk of an incorrect result increases due to possible contamination of the biopsy sample with sperm or granulosa cells adhering to the external surface of the embryo.

12. MitoScore:

High MitoScore values could indicate that the implantation potential of the embryo is low, but do not suggest abnormalities in the embryo. MitoScore does not provide information on the health of the embryo, and all the embryos diagnosed as chromosomally normal are considered potential candidates for transfer, regardless of their MitoScore value.

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ADDITIONAL INFORMATION CONCERNING PGT-SR FOR STRUCTURAL REARRANGEMENTS

DESCRIPTION, PURPOSE AND ADVANTAGES OF PERFORMING THE ANALYSIS

Preimplantation Genetic Testing for Structural Rearrangements (PGT-SR) is offered to patients who, before IVF treatment, find out that one of the partners is a carrier of a balanced structural rearrangement, such as a translocation or inversion. The information regarding aneuploidies described for PGT-A also applies for PGT-SR (please see above sections), with the following modifications:

Translocations and inversions are two types of structural chromosome rearrangements:

- An individual with an inversion has a segment of a chromosome which has changed position within that chromosome.
- A translocation is caused by the transfer of genetic material between chromosomes.

The carriers of balanced structural rearrangements present abnormalities in the structure of the chromosomes, without gains or losses in chromosomal material.

The risk factors of being a carrier of a balanced translocation or inversion include unexplained male infertility (low sperm count), implantation failure, recurring miscarriages, and family history of having offspring born with abnormalities.

In carriers of balanced structural rearrangements, there is a risk of producing eggs and sperm with unbalanced chromosomal alterations which could be transmitted to the offspring. In general, a carrier of a balanced structural rearrangement does not have health problems, although in some cases they may have difficulty conceiving. The embryos of carriers of balanced structural rearrangements may present unbalanced structural rearrangements (gain or loss of a chromosome segment), which may lead to implantation failure, miscarriage, or children born with mental and/or physical problems. If the children inherit the balanced structural rearrangement, they should not have health problems, just like their carrier parent(s).

The identification of embryos which have inherited an unbalanced structural rearrangement may help patients and clinicians to decide which embryos to transfer.

PROCEDURES, RISKS AND LIMITATIONS

The PGT-SR process using NGS will be carried out in a similar manner to PGT-A (see previous sections), using the same biological sample. For the detection of these chromosomal imbalances, an optimised NGS platform is used to detect imbalances greater than 6 Mb, or FISH technology (Fluorescence in situ hybridization, in day 3 embryo biopsy with nucleus fixed on a slide) for imbalances smaller than 6 Mb, wherever possible. If using FISH technology, it will be necessary to carry out a previous blood test on the carrier of the structural rearrangement. The unbalanced structural rearrangement is identified as gains and/or losses of segments of the ends of the chromosomes involved in the structural rearrangement.

Before planning a PGT-SR cycle, the couple must provide their prescribing clinician with a report on the karyotype of the carrier of the balanced structural rearrangement so that it can be subsequently reviewed by Igenomix staff, who will then advise on the appropriate protocol and/or request additional tests if necessary.

The risks and limitations described above for PGT-A also apply to PGT-SR. However, there are additional specific limitations of PGT-SR set out below:

1. PGT-SR using NGS does not allow us to detect chromosomal imbalances below 6 Mb.
2. PGT-SR using FISH on blastomere cells taken from day-3 embryos will be done at our headquarters laboratory in Spain and has specific limitations, including: (i) it cannot detect gains or losses (aneuploidies) of chromosomes other than those involved in the structural rearrangement under study. If required, an additional biopsy at day-5 from the developing embryo may be requested for general aneuploidy screening (PGT-A) using NGS; (ii) Inconclusive results in the case of poor-quality nuclei fixed on a slide.
3. PGT-SR does not allow us to differentiate between completely normal embryos and carrier embryos having a balanced structural rearrangement (same as the carrier parent(s)).

The turn-around-time for PGT-SR is the same as PGT-A

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.co.uk, 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 be removed from any publication; (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 be removed from any publication; (5) Personally address any doubts or suggestions made by the patient during the process and monitor the proper

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performance and resolution of the test, including the indefinite retention of your data, except where local laws of the applicable jurisdiction state otherwise; and (6) Contact you in the future to request an evaluation of the services received, send commercial communications (including 'cross-selling' and 'upselling') from associated companies, and also to invite you to participate in market research and the development of new products.

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 certified with 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.

Pursuant to the laws on the Protection of Personal Data[i], 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, restriction, portability, by sending an email to privacy@igenomix.com, providing proof of the requesting party's identity.

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 consent to an embryo biopsy being performed (PGT-A or PGT-SR) and to a blood sample being taken if required (PGT-SR), for the purpose of sending these samples to the Igenomix facilities so that the analysis can be performed.

I also accept that the results of the test(s) may be passed on to my clinician, so that he or she can advise me correspondingly on the suitable treatment to follow.

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_____

Patient's signature_____ Date: _____/_____/_____

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_____

Partner's signature_____ Date: _____/_____/_____

[i] **For non-US patients:** customers residing outside the United States under certain jurisdictions 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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