INFORMED CONSENT FOR A STUDY PRIOR TO PREIMPLANTATION GENETIC TESTING FOR MONOGENIC DISEASES (PRE-PGT-M)

DESCRIPTION, PURPOSE AND ADVANTAGES OF PERFORMING THE ANALYSIS

Pre-PGT-M entails conducting a genetic study on DNA samples from the couple as well as on other family members (where possible) prior to undertaking Preimplantation Genetic Testing for Monogenic Diseases (PGT-M). The aim is to confirm that PGT-M will be feasible and to determine the best testing strategy to be used on the embryos. PGT-M is used to analyse embryos for a specific genetic disorder before implantation.

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 female and an XY pair for a 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 transmitted by the egg and the other by 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 his/her 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. Two parent carriers have a 25% risk of having a child with the genetic disease.

iii. Genetic diseases associated with gender, normally caused by mutations in the X chromosome. The majority of these sex-linked diseases are recessive and mainly affect males; however, some may be dominant and also affect females in a different way.

Pre-PGT-M will assess whether there are sufficient informative markers (informativity check) linked to a gene in the patient couple and any available suitable family members. In certain cases, pre-PGT-M will include the additional design of a mutation detection strategy that directly interrogates the mutation of interest.

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 with a significant family history of a specific genetic disease to considerably reduce the transmission risk of such disease in their future progeny. Before undertaking PGT-M, pre-PGT-M must be conducted, which establishes the testing strategy to be carried out when performing PGT-M.

PROCEDURE, RISKS AND LIMITATIONS

There are several stages in the pre-PGT-M process:

1. Receipt of initial referral, including genetics reports for patients and any suitable family member(s)
2. Case review, acceptance and request for pre-PGT-M requisition form and required samples
3. Receipt of pre-PGT-M requisition form
4. Receipt and extraction of DNA from biological samples (e,g, blood, buccal sample)
5. “Informativity check” and the design of a mutation detection strategy whenever needed
6. Determination of the feasibility of PGT-M and the strategy to follow
7. Completion and release (where requested by the clinic) of pre-PGT-M report and confirmation issued to the clinic that pre-PGT-M has been completed

Biological samples cannot be processed without the documentation described in points 1 and 3 above. 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 results reports are strictly confidential.

The biological samples (blood or buccal cells) to be used in the genetic analysis, will be obtained using standard techniques with little or no risk to health.

The upper-limit of the time-frame for the reporting of pre-PGT-M results is 6 weeks. The period will commence once Igenomix has received the sample, as well as all those from family members that Igenomix identified as being necessary in the consultation held prior to the acceptance of the case. A small percentage of samples may be delayed due to unforeseeable causes. Should this occur, the corresponding clinic in charge will be notified.

While there are considerable benefits to the test, limitations exist and are described below:

a) The test(s) will be strictly limited to detect the specific disease/mutation stated in the genetics report. There is a small probability that the test will not be conclusive and subsequently, PGT-M could not be offered (e.g. lack of information markers, failure to detect the mutation of interest, consanguinity and other factors).
b) Family samples will be used to establish the "haplotype" linked to the disease and not for the test itself. As such, a corresponding report will not be issued for these samples.

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; 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 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[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 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

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 content to the taking of a blood or buccal cell sample in the assisted reproduction Centre/Clinic which I have attended. I also consent to the sample being sent to Igenomix facilities for the purpose of carrying out the aforementioned test(s).

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 IVF treatment.

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 signature and full name_____ _____ 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 signature and full name_____ Date: _____/_____/_____

Partner's date of birth_____/_____/_____