

PRE-IMPLANTATION GENETIC TESTING FOR MONOGENIC DISORDERS (PGT-M)

Purpose & Introduction :

Pre-implantation Genetic Testing for Monogenic disorders (PGT-M) is a technique used in conjunction with In- Vitro fertilization (IVF) to detect embryos with a condition caused by a known single gene variant/s. Embryos that are affected by a genetic condition can lead to birth of a child with physical and/or cognitive problems. These could also be lethal conditions. The purpose of PGT-M is to help prevent adverse outcomes by identifying affected embryos in the laboratory and transferring normal embryos.

Method :

The NGS PGT-M method (preimplantation genetic diagnosis based on next-generation sequencing platform) uses the most up-to-date technique of human genome sequencing (reading of genetic information) for testing embryos and opens up new diagnostic possibilities. It is used as a part of in vitro fertilization and provides comprehensive information concerning embryo's DNA with regard to genetic disorder/ known disease causing variant. It provides physicians with a unique opportunity to help couples who are at an increased risk of having offsprings with genetic abnormalities.

Who should opt for PGT-M?:

- Previous child with a genetic disorder with a known genetic mutation.
- Parents are carriers for monogenic disorders including-
- Lethal autosomal recessive conditions
- Autosomal dominant conditions
- X linked conditions

Preimplantation Genetic Testing for Monogenic disorders with Next Generation Sequencing (NGS PGT-M):

Next Generation Sequencing (NGS) is the latest technology available for preimplantation genetic testing for monogenic/single gene defects (PGT-M) and preimplantation genetic testing for aneuploidies (PGT-A). NGS has various advantages over other techniques including-

- High accuracy
- High number of probes,
- Not susceptible to signal saturation, and signal noise.
- Detection of mosaicism
- **Credible result:** Within PGT-M NGS, each sample is assigned an additional molecular code, eliminating the possibility of error since the moment of collecting material from the embryo. In addition, the test credibility is enhanced by a direct connection of DNA reading with the obtained information.
- **Embryo safety-reducing the number of biopsies for the diagnosis:** Usually just one embryo biopsy is sufficient to obtain a reliable result. In the case of existing methods, occasionally, the biopsy and the test has to be repeated.
- **Test in combination:** The same embryo biopsy can be used to carry out PGT-M to select healthy embryos not having the monogenic disorder followed by PGT-A to look at chromosomal abnormalities and select healthy embryos.
- **NGS method is considered to be referential for all the other techniques:** DNA sequencing is described as the reference method (model for others), mainly due to the direct nature of the genetic material reading. Other methods (FISH and microarrays) use markers and light as change markers and indirectly test the genetic material. For this reason, these methods are currently being abandoned for the use of NGS.
- **Lower costs of test:** The special design of the Next Generation Sequencing allows for a significant reduction in the cost of tests in comparison with existing methods. Due to which, we increase the availability of PGT-M preimplantation genetic diagnosis among patients.

Risks & Limitations:

- Preimplantation genetic testing for monogenic disorder (PGT-M) only screens for specific known disease causing variant/s. It will not rule out other genetic disorders. Also, in 1-5% of cases, the results of PGT-M may be inconclusive. In other words, the test might fail to pick up an abnormality that exists or no signal was visible.
- The cells retrieved from embryo biopsy are sent via courier to Neuberg Centre for Genomic Medicine (NCGM), Ahmedabad for analysis. Certain unforeseen 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. NCGM is not responsible for any loss or damage to a sample during transport.
- There are a number of factors due to which the results of PGT-M are not 100% accurate. Some of these being-
 - The test relies on a genetic report obtained prior to PGT-M that describes the specific mutation(s) causing the familial disease. On evaluation of incorrect mutation(s), the testing will not be accurate.
 - Background contamination from other embryos/ individuals involved in the PGT-M procedure may reduce the accuracy of the test.
 - A phenomenon termed as Allele drop-out, which results from testing a small number of single cells may reduce the efficiency of the test
 - The presence of recombination that may affect the accuracy of the result cannot be completely ruled out
- Preimplantation genetic testing is limited by the technology and the number of cells examined. Therefore, it is recommended that any patient who conceives after this technique should consider routine prenatal diagnosis through amniocentesis to confirm PGT-M results. Congenital abnormalities, birth defects, genetic abnormalities, mental retardation and other possible deviations from normal can occur following In Vitro Fertilization (IVF), & may also occur following the transfer of embryos that have undergone PGT-M. Damage or destruction of the embryo is also a potential risk of PGT-M, although this risk is small. We have reviewed the costs of treatment and will be personally responsible for all expenses. The expenses include, but are not limited to, hospital charges, laboratory charges, and physician professional fees.

We have read the general information for PGT-M and we understand that the methods include:

- Removal (biopsy) of 6-8cells from suitable embryos five days after insemination by ICSI.
- The biopsied cells will be tested for the disease causing variant/s for which our children are at risk
- The result may show that all the embryos are affected.
- In an unlikely event, PGT-M testing fails to yield any results, we have the choice of whether or not to transfer embryos that may or may not be affected with the genetic condition.
- In circumstances of autosomal recessive disorders which require both copies with disease causing variant/s to be inherited embryos that are determined to have a single alteration or both normal copies will most likely be unaffected and may be transferred based of clinician's discretion.
- X-Linked recessive disorders are conditions where one copy of X chromosome with the disease causing variant is enough to cause the disorder in males. PGT-M will be able to screen X-Linked disorder and report on affected embryos. However, other embryos will be given as normal. We will not be able to differentiate between normal and carrier embryos.

All of our questions have been answered, and we know that any future questions concerning our care will be answered by our physician. We have been assured that all information about us obtained during these procedures will be handled confidentially and that neither our identity nor specific medical details will be revealed by clinic personnel without our consent.

After the embryo transfer, we wish that those embryos that have been determined to be affected with disease, and therefore not frozen for future transfer, be sent to the Neuberg Centre for Genomic Medicine to confirm affected status. These embryos will be discarded after conformational testing.

We are aware that PGT-M testing has an estimated 5% risk of misdiagnosis; therefore, no guarantee has been given to us regarding the outcome of this test. We have been strongly advised to have prenatal diagnosis testing to confirm the single-gene PGT-M test results, and we understand the risk associated with not having prenatal testing. We also understand the risks involved with chorionic villus sampling (CVS) and amniocentesis. If we elect to have prenatal testing performed, we agree to have the sample tested at the Neuberg Centre for Genomic Medicine.

Neuberg Centre for Genomic Medicine (NCGM)

Near GTPL House, Opp. Armedia, Sindhu Bhavan Road, Bodakdev, Ahmedabad 380059
Phone: +91-6357244307, 079-61618111 | Email: contact@ncgmglobal.com | Web: www.ncgmglobal.com

We have been informed that some studies report that congenital abnormalities, birth defects, genetic abnormalities, mental retardation, and/or other possible differences may occur in children born following IVF, cell biopsy, and PGT-M testing. We understand that these problems also occur in 3-5% of children resulting from natural conception without PGT-M testing.

We are aware that additional genetic alterations associated with our specific disease but not identified in us might exist in an embryo and will not be examined.

We have been informed of the possible risks and consequences associated with PGT-M testing.

NON-DISCLOSURE

We have had the opportunity to ask questions and discuss the procedure and we have received satisfactory answers. We consent to these procedures. Your identity and your all personal information shall be kept confidential. Relevant authorities will be permitted access to this information by the law of the applicable jurisdiction. The Health Authorities shall have access to them to review medical records. As part of their occupational duties, the personnel with access to your personal details shall be subject to permanent professional secrecy.

ACKNOWLEDGEMENT

- I acknowledge that
- I have read and understood this written material.
 - I understand the purpose, risks and benefits of this procedure.
 - I am aware that there may be other risks and complications, not discussed, that may occur. During the course of the procedure, unforeseen conditions may be revealed requiring the performance of additional procedures.
 - Technical problems with the instrumentation may prevent the completion of the procedure. No guarantees or promises have been made to me concerning the results of this procedure or any treatment that may be required as a result of this procedure.

PATIENT CONSENT

This procedure has been explained to me in a language that I understand. I have been given the opportunity to consider other options and alternatives. I have been counselled about the risks, benefits and limitations of this test. I willingly request NCGM Supratech to carry out this test. I opt in to donate extra DNA material, if available, for research.

I have read and have received a copy of the consent form.

Husband Signature

Husband Name

Signature

Partner Name

Date: DD/MM/YY

Wife Signature

Wife Name

Signature

Partner Name

Date: DD/MM/YY

DOCTOR AUTHORIZATION

I certify that the information on this form is correct to the best of my knowledge. I have requested this test based on my professional clinical judgement. I have counseled the patient about the possible testing outcomes and have explained the limitations of this test. I agree to share any other information if requested by the providers.

Doctor Signature

Doctor Name

Date: DD/MM/YY

Embryologist Signature

Embryologist Name

Date: DD/MM/YY

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