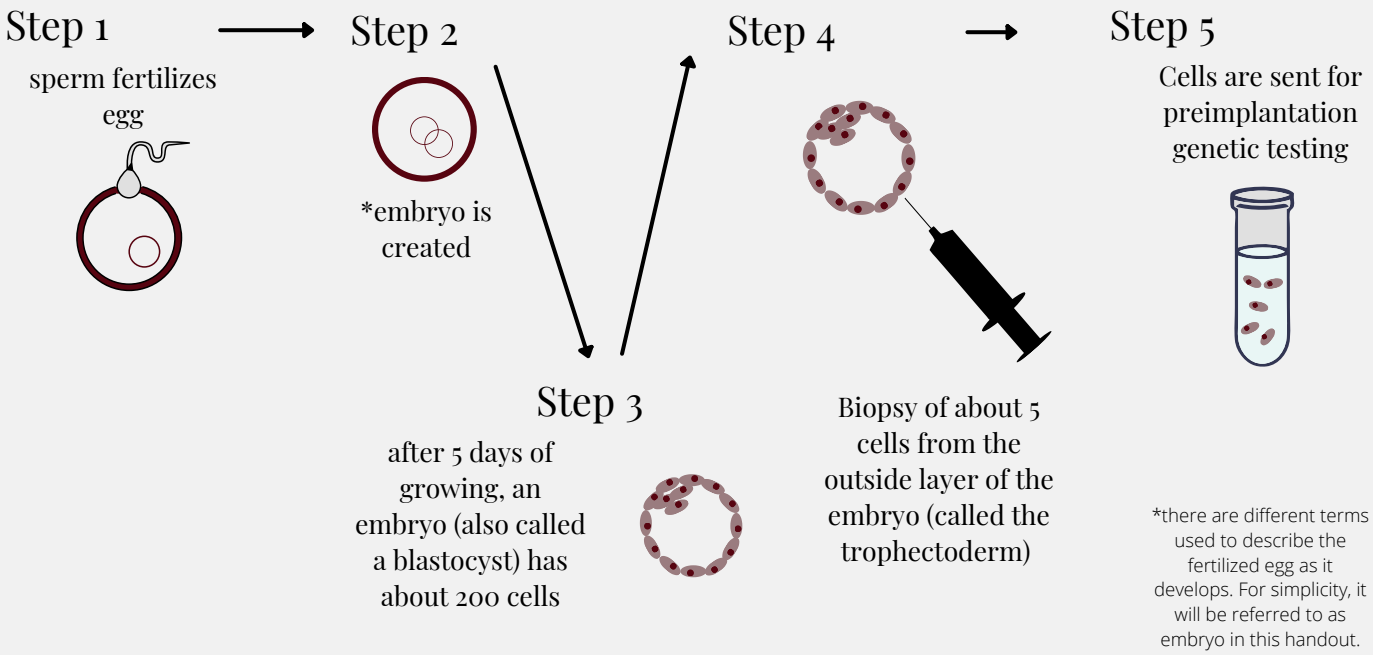
What to Expect: PGT-M

Preimplantation genetic testing is performed on embryos created through in-vitro fertilization (IVF). An embryo is created after an egg is fertilized by a sperm. After fertilization, embryos develop from a single cell into a cluster of around 200 cells. In order to perform the genetic analysis, a few cells are biopsied from the embryo and sent to a genetic testing laboratory. The laboratory will run the PGT-M analysis to generate a report for each sample sent in. The report will help guide which embryos are expected to have the condition and which are not.

The main purpose of PGT-M is to carefully select and implant embryos that do not carry the specific genetic condition of concern. This helps increase the chances of the birth of a baby without the genetic condition.



PGT-M is a genetic test that can check for one or a few specific conditions if there is a known chance of passing them on. However, it is important to know that PGT-M does not assess for all possible genetic conditions. It is a specialized test focused on specific conditions of concern.

Even though PGT-M is a helpful tool, it is not foolproof. There is a small possibility of getting false results, both negative (missing a condition) or positive (indicating a condition that is not present). That's why it's still important to consider other testing options during pregnancy or after a baby is born.

To test embryos with PGT-M, several steps need to be followed. This includes going through the IVF process and developing the specific PGT-M test for your family's genetic situation. The development of the PGT-M test can take some time, usually between 4 to 12 weeks. Additional appointments and testing may also be necessary throughout the process.

Why is PGT-M different from other genetic tests?

PGT-M stands out from other genetic tests due to two primary reasons. Firstly, PGT-M is a highly specialized assessment that is tailored specifically to each family's genetics. Unlike other genetic tests, in which everyone uses the same assessment, PGT-M creates a unique test for every family. Even if a PGT-M test has been developed for a particular condition in the past, it doesn't necessarily apply to your family's genetic makeup.

Therefore, it's important to note that PGT-M may not be suitable or feasible for every family's situation and certain requirements must be met. The initial step in the PGT-M process involves a comprehensive case review, where genetic test reports and family information are carefully examined to determine if PGT-M is a viable option.

Secondly, PGT-M differs from other genetic tests in that it focuses on tracking a specific variant that may be passed on from a couple or individual to their embryos. This is achieved through a method called linkage analysis. In contrast, many other genetic tests, such as carrier screening tests, involve sequencing a person's DNA to identify any changes or variations in the genes that could impact their function. It's akin to reading through the instruction manual of a person's body to identify errors or missing information whereas linkage analysis is like comparing two editions of the manual to see if there are any special markings or changes that help us tell them apart.

By utilizing linkage analysis, PGT-M enables the identification and tracking of specific variants within a family's genetic makeup.

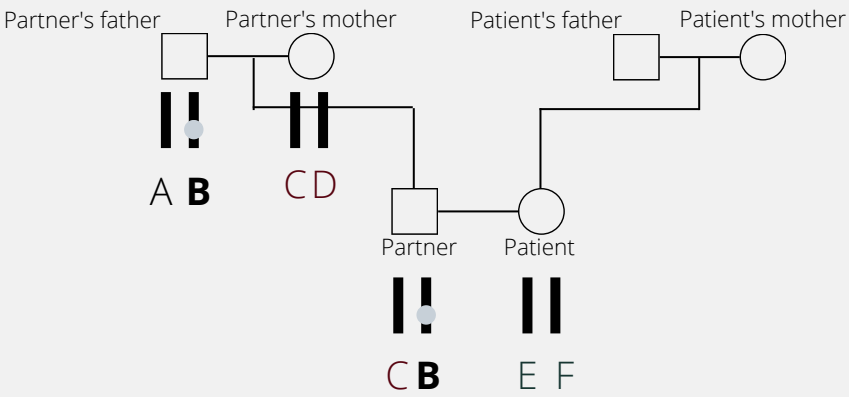
What is linkage analysis?

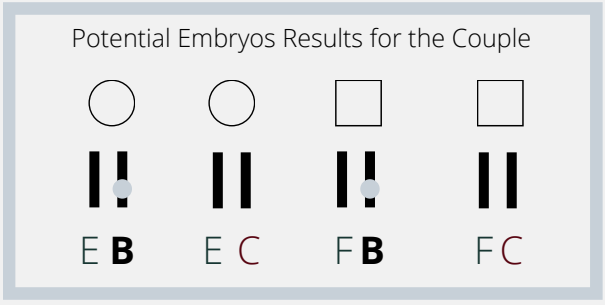
For most of our genes, we all have two copies. One we inherited from our mom or egg donor and the other from our dad or sperm donor. Linkage analysis is the ability to distinguish between the two gene copies. By distinguishing between the two gene copies, linkage analysis will be able to discern which gene copy is the one with the variant and the gene copy without the variant.

Linkage analysis involves examining the DNA sequence of a person to identify distinctive qualities or markers that help distinguish between the two gene copies. These markers can be specific changes in the genes that do not cause harm to the gene's function but aid in differentiating the gene copies. Multiple markers are identified to create a "marker profile" for each gene copy. Then, during embryo evaluation, these marker profiles are analyzed to determine which gene copy was inherited.

It's important to note that performing linkage analysis requires the involvement of a second generation. For instance, if a person has a known genetic condition and their father is also impacted by the same condition, the DNA of the person's parents can be compared to their own DNA. This comparison helps identify the specific gene copy responsible for the condition and the corresponding marker profiles.

The next page has a visual example of how linkage analysis is used.





Key:

These two lines represent the two gene copies that an individual has. One of these gene copies has a variant, which is represented by the circle. It is this gene copy with the variant that causes the genetic condition in the family shown on the right.

A, B, C, D, E, F are used to refer to the marker profiles that have been linked to these alleles.

The above diagram is called a pedigree. It illustrates the relationships among the patient, her parents, her partner, and his parents. The squares represent genetic males, while the circles represent genetic females. In this diagram, the patient is a genetic female, and her partner is also shown.

The partner's father has marker profiles A and **B**, while his mother has marker profiles C and D. When the partner was conceived, he inherited his father's **B** marker profile and his mother's C marker profile. The partner and his father have both been diagnosed with the genetic condition. Given both the partner and father have the genetic condition, the **B** marker profile is considered to be *linked* to the variant that causes the condition.

Now, the couple wants to test their embryos for this genetic condition. There are two possible options for the inheritance of marker profiles in the embryos from the partner. 50% of the embryos will inherit the partner's **B** marker profile, while the other 50% will inherit the C marker profile. You'll notice that the potential embryo results will also have a 50% chance to inherit the E or F marker profile that has been established for the patient. Neither the E or F marker profile have a variant of concern.

It is presumed that the embryos inheriting the **B** marker profile will have the genetic condition because this marker profile has been linked to the disease variant.

Please note that this is a simplified explanation for illustrative purposes. In some cases, there will be egg or sperm donors or other family structures not shown. The actual process and analysis of PGT-M involve more detailed genetic assessments.

There are several steps involved in starting and completing the PGT-M process. These steps may differ depending on the laboratory conducting the testing.

Before:

- ☐ **Genetic Testing:** It is necessary to undergo genetic testing to identify the specific gene and variant responsible for the condition. Both genetic contributors will need to provide genetic test reports, unless the condition follows autosomal dominant or X-linked inheritance, in which case the genetic report of the person with the condition is required. Genetic testing for other family members, such as parents or children, can also be helpful in designing the testing process.

- ☐ **Choose a Clinic:** Find a clinic that offers in vitro fertilization (IVF) services and collaborates with a genetic testing laboratory that performs preimplantation genetic testing.

- ☐ **Insurance Coverage:** Contact your insurance company to inquire about their coverage for genetic testing and IVF.

During:

- ☐ **Initial Evaluation:** Your clinic will need to send an order form and your genetic testing results to the laboratory. This is done to assess if your case is suitable for PGT-M technology. In some cases, additional genetic testing may be required for a better understanding of your DNA or a consultation with a genetics provider to discuss specific details of your report.

- ☐ **Consultation with a Genetic Counselor:** If your case is deemed feasible, you will typically be scheduled for a consultation with a genetic counselor from the lab. The purpose of this consultation is to discuss the logistics of PGT-M and create a plan tailored to your unique situation and genetics. If you don't have any relatives available for test design, the genetic counselor can explore alternative options with you, if available.

- ☐ **Genetic Testing for Relatives:** If other relatives are participating in the test design, they may be asked to undergo genetic testing with an external lab if they haven't done so already.

- ☐ **DNA Kits and Collection:** Once all the necessary documentation is received, the lab will send out DNA kits to you, your partner/donor, and any participating relatives. These kits will be used to collect the DNA samples required for the testing.

- ☐ **Test Design:** After receiving all the DNA samples, the lab will proceed with the test design process. This step involves creating a personalized test based on your specific genetic information. The turnaround time for test design can vary, typically ranging from 4 to 12 weeks.

- ☐ **Notification and Clinic Collaboration:** Once the test design is complete, you and your clinic will be notified. Most of the time, test designs are successful. However, there may be instances where a test design cannot be created due to certain factors.

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