# PGT-A Testing: What your patients need to know before deciding

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## Preimplantation Genetic Testing

Preimplantation genetic testing (PGT) is a blanket term that applies to any genetic testing performed on an embryo prior to uterine transfer. This testing is performed following in vitro fertilization (IVF), typically at the blastocyst stage. Depending upon their specific indication, several subtypes of PGT that exist are as follows:

- PGT-*A* refers to the testing of embryos for *A*neuploidy, which includes both full and partial chromosome abnormalities.

- PGT-*M* refers to the testing of an embryo for *M*onogenic (single-gene) disorder inherited from one or both parents (i.e., Cystic Fibrosis, Sickle Cell disease).

- PGT-*SR* refers to testing an embryo based on a *S*tructural *R*earrangement in parental chromosomes (i.e., translocations, inversions).

PGT-A is a consideration for all patients planning an IVF cycle, as chromosome abnormalities are a universal risk. In contrast, PGT-M and PGT-SR are only indicated for a small subset of patients.

Over the past decade, the use of PGT-A for embryo selection in IVF cycles has increased dramatically such that it is now commonplace for clinics to offer, or even require, this add-on genetic testing as part of their IVF process. The average patient typically is given information regarding the complexities, benefits, and limitations of PGT-A testing, which can be overwhelming. In fact, many patients regret doing (or not doing) PGT-A testing when questioned at a later time[1].

Coming from the perspective of a genetic counselor with over a decade of working with IVF patients, the following questions can help patients make an informed decision about whether PGT-A testing is right for them.

## What is a PGT-A test and is it applicable to your patient?

PGT-A tests for *chromosomal abnormalities* in the embryo. Normally, every human cell has 23 pairs of chromosomes, for a total of 46 chromosomes. Aneuploidy is a state where there are extra (trisomy) or missing (monosomy) chromosomes. For most labs offering PGT-A, the test is validated to detect chromosome abnormalities larger than 10 Megabases (MB), where an MB is equal to 1 million DNA base pairs. Chromosomes range in size from about 35 MB to 250 MB. Therefore, 10 MB could represent up to 25% of the entire chromosome depending on the chromosome[2]. In the majority of cases, aneuploidy occurs randomly due to nondisjunction errors during meiosis. While aneuploidy is a risk to all pregnancies, the risk increases with maternal age. Selecting to transfer embryos with euploid (normal chromosomes) is thought to maximize the success rate per transfer and decrease the miscarriage rate.

## What doesn't PGT-A test?

PGT-A does not provide results on *anything other than large chromosomal abnormalities*. As noted above, this testing can detect chromosome abnormalities that are ≥ 10 MB. PGT-A would *not* detect any common microdeletion or microduplication syndromes such as 22q11 deletion syndrome (DiGeorge), Williams Syndrome, or Prader-Willi syndrome. Additionally, PGT-A does *not* test for single-gene disorders such as Cystic Fibrosis, Spinal Muscular Atrophy, Sickle cell disease, or Fragile X syndrome. This is the reason that parental carrier screening is so important prior to IVF, so that those couples in need of single gene embryo testing are identified and may consider PGT-M testing. Furthermore, PGT-A will *not* test for multifactorial conditions, which may run in families, caused by a combination of genetic predisposition and non-genetic factors (i.e., autistic spectrum disorder, heart disease, diabetes). Finally, PGT-A will *not* detect idiopathic congenital birth defects, as the majority of birth defects occur sporadically and are not related to a chromosomal abnormality.

## How accurate is the testing?

Most PGT labs report an accuracy rate of 97-98%, meaning there remains a 2-3% rate of a false negative or false-positive result[3,4]. A false negative result means that an embryo deemed "normal" by PGT-A could have a chromosomal abnormality. For this reason, medical societies agree that patients who underwent PGT-A testing and transferred a "euploid" embryo should still be offered routine chromosome screening and testing options available during pregnancy (cell-free fetal DNA, chorionic villus sampling, amniocentesis), as the risk of chromosome abnormalities have been *reduced*, but not eliminated[5]. False-positive results refer to an embryo given an abnormal result by PGT-A, when, in fact, the cells in the inner cell

mass had normal (or primarily normal) chromosomes and may have resulted in a healthy child. Typically these errors result in the embryos not being transferred, possibly leading a couple to pursue a new IVF cycle or, in some cases, to give up on biological parentage.

The primary reason for the reduced accuracy of PGT-A is due to sampling error. The embryo biopsy is typically removed from the trophectoderm (TE) at the blastocyst stage and may include anywhere from 2-10 cells. If this small sampling of TE cells is not representative of the entire trophectoderm, or more importantly, of the inner cell mass, results of PGT-A testing will not be accurate.

## What if patients get anormal results?

Most patients do not realize just how common aneuploidy in embryos is at the blastocyst stage, even in young women. This is likely because the statistics we typically hear about are the likelihood of a chromosome abnormality *in a live birth*. However, only a very small percent of aneuploid embryos at the blastocyst stage survive to birth, with the majority resulting in failed implantation or missed abortion[6,7]. Therefore, the discrepancy between the aneuploidy rate expected at birth versus that at embryo biopsy is enormous. For example, the risk for a 30-year-old to have a live birth with any chromosome abnormality is estimated to be 1 in 384, or 0.26%[8]. In comparison, numbers provided by one PGT-A lab indicate that the risk of a blastocyst embryo having an aneuploid result for PGT-A when the egg source is a 30-year-old is 34% (n=8,499 embryos)[9]! For a woman of advanced maternal age, the likelihood of aneuploid results in PGT-A testing is even higher. Therefore, when testing several embryos, your patient needs to know that it is *highly likely* that some of her PGT-A results will be abnormal. Think about it, if this were not the case and we expected all normal results, why would they even *need* PGT-A testing?

## What if there are no embryos suitable for transfer?

Is your patient a low responder? Over 40? Is there significant male factor? It is important for them to know it is possible they will not have any embryos with normal results deemed "suitable to transfer." Statistics from the same PGT lab indicates that an average of 75% of embryos from a 41-year-old will be returned with aneuploid results (n=7,258) and that 34% of women in this age group will have 3 or less embryos available for testing[9]. The likelihood of a patient in this age group or a low responder in any age group to have no euploid results is substantial. For some patients, whose main goal is to prevent failed implantation or pregnancy loss, these statistics may be palatable, as they would prefer to have *no* transfer than an *unsuccessful* transfer. However, for others, PGT-A testing is chosen with the assumption that there will be "good" embryos to transfer. In the event of no embryos for transfer, understanding the possibility of a false positive result, some patients will desire to transfer an embryo with abnormal results, if the alternative is no transfer at all. Is this an option for your patient based on clinic policy?

## Will Mosaic results be available?

*Mosaicism*, defined as the presence of more than one chromosomally distinct cell line in a sample, is very common in PGT-A results and poses a risk of misdiagnosis, as the cells biopsied from the trophectoderm may not always be representative of the inner cell mass. Limited outcome data of transfer of embryos with a mosaic PGT-A results indicate that embryos with mosaic PGT-A results have lower potential to result in a healthy child than embryos with euploid PGT-A results, yet higher potential than that of embryos with aneuploid results[10-15]. In fact, a small and growing number of apparently-healthy live births have also been observed as outcomes of mosaic transfers.

Patients need to know ahead of time whether a mosaic result is a possibility. Does your clinic report mosaicism? Some clinics choose to have laboratories report all results as either normal or abnormal (which would include mosaic results) and other clinics ask for abnormal and mosaic results to be listed separately. Some patients have never heard of a mosaic result and do not understand that there is a possibility their results will not be black and white, but rather grey. Other savvy patients are very aware of the complexities surrounding mosaic results and may be undergoing PGT-A with the expectation that this information *will* be provided to them. If your clinic does report mosaic results, what is the policy regarding transfer of mosaic results if no euploid embryos available? Different clinics have different policies on this issue and it is something that patients need to be made aware of *before* deciding to do (or not do) PGT-A testing. Too often this policy is only discussed *after* PGT-A results are returned and patients without euploid results are asking to transfer embryos with non-euploid results.

## Does PGT-A testing have to be YES or NO?

PGT-A is a numbers game. The more embryos available for testing, the higher the likelihood of having embryos with euploid results. For high responders with numerous embryos available, euploid results are likely and PGT-A helps clinics to prioritize which embryo(s) to transfer first. However, for couples expected to have a low number of embryos available, the likelihood of no euploid results from a PGT-A cycle is very real. With this in mind, does the decision to do (or not do) PGT-A testing have to be all or none? Is it possible for a couple to choose to do PGT-A testing if they have *X* number of embryos but to decline testing if they only have *Y* or less embryos? If this is an option, are your patients aware of it?

## What is your patient's Goal?

Overall, healthcare providers in the reproductive clinic need to assess, *what is my patient's main goal of undergoing PGT-A*? Do they have a history of recurrent pregnancy loss and want to do anything and everything to avoid another pregnancy loss? PGT-A absolutely makes sense for this couple. Is it important to them to achieve pregnancy in the fastest time frame? For those with multiple embryos, PGT-A may help them get their desired result with fewer transfers. Are they older or low responders whose number one goal is to maximize their chance of biological parentage? The false positive risk of PGT-A testing may work against them in achieving this goal, as it may result in discarding of embryos with potential to result in a healthy child.

## Conclusion

PGT-A testing is an available tool that clinics have which can help to prioritize embryos for transfer and provides information about the likelihood of an embryo resulting in a successful pregnancy and healthy child. However, like many tools, this is an imperfect tool with extreme variability, such that results cannot accurately be predicted ahead of time. Patients need to be prepared not only for normal and abnormal results, but for the possibility of other situations including mosaic results with unclear clinical implications, no embryos available for transfer, and both false-positive and false-negative results. Doctors often do not have the time to explain genetic testing in detail prior to testing. You can provide great service to your patients by discussing the questions in this article and enabling them to fully understand whether or not this testing will meet their goals.

## About the author

**Jamie K. Dokson, MS, LCGC** is a multi-state licensed genetic counselor with many years of experience working in clinical and laboratory genetic counseling. Jamie received her undergraduate degree in both Psychology and Biomedical ethics from Brown University in 2001. After graduation, she spent three years working as a clinical researcher in an ovarian cancer screening study at Massachusetts General Hospital. In 2007, Jamie graduated from Johns Hopkins University in Baltimore with her Master of Science in Genetic Counseling. She has been board certified in genetic counseling by the American Board of Genetic Counseling since 2009. From 2007-2009 Jamie served as a prenatal genetic counselor and member of the Hospital Ethics Committee at a hospital in Baltimore. In 2009, Jamie moved to Atlanta where she joined a large private fertility practice. She spent the next decade working in Reproductive Genetics with specialty focus in carrier screening, preimplantation genetic testing (PGT), and gamete donor screening. During this time Jamie also served as the Director of Genetic Services for an international donor egg bank and was in charge of genetic screening protocols for prospective gamete donors. Jamie is an Adjunct Instructor of Human Genetics at Emory University Department of Human Genetics and has served as a clinical supervisor for genetic counseling graduate students over many years. Jamie is an active member of the National Society of Genetic Counselors (NSGC) and American Society for Reproductive Medicine (ASRM). In 2015 Jamie opened her own private practice, Navigate Genetic Counseling, where she focuses on conducting genetic counseling services via Telegenetics with an emphasis on reproductive genetics, in addition to cancer genetics and proactive genetic testing. Jamie is passionate about helping individuals and families understand complex genetic risk information to make informed decisions based on their specific values and goals.

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