The Past, Present, and Future of Preimplantation Genetic Testing

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KEYWORDS

• Aneuploidy • Embryo research • Preimplantation genetic diagnosis (PGD)
• Preimplantation genetic screening (PGS) • Preimplantation genetic testing (PGT)
• Single-gene disorder

KEY POINTS

- Preimplantation genetic screening (PGS) has helped many individuals prevent the birth of children with severe genetic diseases and also the need for selective abortion associated with postgravid antenatal screening techniques.
- Given the disadvantages associated with cleavage-stage biopsy for preimplantation genetic testing (PGT), most centers have adopted trophectoderm biopsy and cryopreservation of tested blastocysts for subsequent transfer as a new clinical paradigm.
- Utilization of newer genetic testing platform for PGS for aneuploidy is becoming an effective way to improve the chances of live birth, especially if elective single-embryo transfer is considered.
- Increasing knowledge of the human embryo and the genetic basis of human disease coupled with the development of these new genetic testing platforms will lead to increased application and use of PGT.

INTRODUCTION

Clinically applicable PGT was first accomplished in 1990, when it was announced that 2 women at risk for transmitting recessive X-linked diseases were pregnant with female fetuses as a result of in vitro fertilization (IVF) followed by embryo biopsy and sexing by polymerase chain reaction (PCR) for the Y chromosome.[1] At present, PGT has been used to identify more than 200 genetic disorders (https://genesisgenetics.org/pgd - What we test for). The indications of PGT include the identification of embryos harboring autosomomal recessive diseases, autosomal dominant diseases, sex chromosome–linked diseases, genetic mutations with important late-onset implications, chromosomal

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structural abnormalities (translocations), chromosomal numeric abnormalities (aneuploidies), and mitochondrial disorders. Additionally, PGT can be used for gender selection for medical (X-linked diseases or nonmendelian disorders with unequal gender distribution) or social (family balancing) reasons. PGT is necessary to identify HLA-matched embryos to permit the creation of a savior sibling whose umbilical cord blood could provide stem cells for a sibling in need of a stem cell transplant. If the sibling's condition is due to a single gene mutation, then concurrent preimplantation genetic diagnosis (PGD) for both HLA matching and absence of the mutation is required.[2]

The techniques and technologies used for PGT have evolved rapidly, providing greater promise for this treatment strategy. In the past, polar bodies from oocytes or 2-pronuclei (2PN) zygotes, or blastomeres from cleavage-stage embryos not older than 3 days post–egg retrieval, were analyzed. More recently, trophectoderm biopsy of day 5 or day 6 blastocyst embryos has replaced day 3 or earlier biopsy. Trophectoderm biopsy provides more genetic material, is less likely to delay embryo development, and is less likely to yield a false-positive result due to mosaicism.[3–10] Previously, fluorescence in situ hybridization (FISH) was used to screen embryos for aneuploidy or diagnose the presence of translocations. This technology was fraught with technical limitations, such as hybridization errors, interpretation error, and ability to test only a few chromosomes. Randomized controlled trials conducted using FISH technique, prior to the advent of trophectoderm biopsy, in women at risk for aneuploidy due to advanced reproductive age, found lower pregnancy rates after embryo biopsy.[11] Recently, several platforms have evolved that are capable of accurately evaluating all 23 chromosome pairs, including comparative genomic hybridization (CGH) microarray, single-nucleotide polymorphism (SNP) microarray, real-time PCR, and next-generation sequencing (NGS). The advent of trophectoderm biopsy and more accurate assays has resulted in a recent resurgence in the use of PGT for aneuploidy screening.[12]

There is no doubt that PGT has helped deliver remarkable gifts to many people; however, its use and application are not without risks or controversy. There is little or no medical or ethical debate about the benefit of PGD in diagnosing embryos at risk for inheriting lethal or significant, diseases, such as cystic fibrosis, Tay-Sachs disease, sickle cell anemia, or Huntington chorea. Medical debate has centered around the use of PGT for aneuploidy screening. Despite absence of medical benefit in improving live birth rates, PGS accounted for approximately 60% of all PGT procedures in Europe in 2009 to 2010.[13] PGT techniques are also used clinically to prevent transmission of genes associated with late-onset diseases, curable diseases, and increased, but not absolute, risk of disease. It is in these areas where many of the ethical concerns with PGT have been debated. The management of devastating late-onset conditions, such as Huntington chorea, poses challenges in disclosing, or hiding, the presence of the Huntington mutation when potentially affected parents choose not to know their status. Creation of a human being for the purpose of being a savior sibling is an area of intense ethical discussion. Another contentious application is the use of PGT to sex embryos for family balancing and to select for specific genetic traits.[14–17] With more and increasing knowledge of the human genome and stem cell biology, the full potential of PGT has yet to be realized. This review discusses the techniques and clinical application of PGT and the debate surrounding its associated uncertainty and expanded use in modern medicine.

HISTORIC PERSPECTIVE AND DEFINITION

In 1986, a group of experts met to discuss the feasibility of prenatal testing in the human preimplantation period to avoid the need for selective abortion associated