



HEALTH SCIENCES

Single-Gene Preimplantation Genetic Diagnosis of Embryos Wake Forest University Health Sciences Clinical Molecular Genetics Laboratory

Purpose

Currently, couples who are at risk for having a child with a genetic disorder have the option of undergoing prenatal testing, such as chorionic villus sampling (CVS) or amniocentesis. In order for these tests to be completed successfully, the specific genetic alteration must have been detected previously either in the parents or a previously affected child. These procedures involve sampling fetal cells from within the womb during the first trimester or second trimester of pregnancy, respectively. The cells are then analyzed to determine whether a specific genetic alteration is present in the developing fetus. For patients at risk of passing on a dominant disorder to their children, natural conception usually carries a 50% chance with each pregnancy that the fetus will be affected by the disease. Couples where both parents are carriers of a recessive disorder generally face a 25% chance with each pregnancy of having an affected child. If a genetic abnormality is detected, parents may face the difficult decision of whether or not to continue the pregnancy. The purpose of single-gene preimplantation genetic diagnosis (PGD) is to greatly reduce the probability of becoming pregnant with an affected fetus as compared to natural conception. Single-gene PGD testing identifies those embryos that are affected with a specific known disease-causing genetic alteration thereby making it possible to prevent them from being transferred to a mother's womb. Although current single-gene PGD methods greatly improve the chances of having an unaffected child, there is no guarantee that a pregnancy initiated after single-gene PGD analysis will be unaffected.

Genetic Testing and Informed Consent Counseling

Single-gene PGD testing will only provide information concerning the specific genetic alteration(s) that the laboratory is made aware of through patient medical records and genetic testing. Any additional genetic alterations associated with a specific disease, but not identified in the patient or her partner, might exist in an embryo and will not be examined. Therefore, a copy of all laboratory reports regarding the at-risk alteration or disease status relevant to the requested single-gene PGD testing is **required** to be sent to the Wake Forest University Health Sciences (WFUHS) Clinical Molecular Genetics Laboratory. Peripheral blood samples from the patient and her partner are also **required** to confirm the disease causing alteration(s) and to optimize the single-gene PGD testing. In addition, a letter or clinic note is **required** from a board-certified/eligible genetic counselor or board-certified/eligible clinical geneticist stating that the patient has received appropriate counseling regarding: 1) In Vitro Fertilization (IVF) and Intracytoplasmic Sperm Injection (ICSI) 2) embryo biopsy 3) single-gene PGD testing 4) prenatal testing. **All required documentation and peripheral blood samples must be sent to the WFUHS Clinical Molecular Genetics Laboratory six to eight weeks prior to initiating the IVF procedure to allow sufficient time to establish testing protocols.**

Procedures

Patients agreeing to have single-gene PGD analysis of their embryos first undergo ovarian stimulation, egg retrieval, and intracytoplasmic sperm injection. When the embryos are approximately three days old a single cell is removed (biopsied) from each embryo and then analyzed for a disease-specific genetic alteration(s). If the biopsied embryonic cell is found to be free of the disease-causing genetic alteration(s), then it is very likely that the embryo it was derived from is also free of the disease.

Embryos found to be unaffected are transferred to the mother or frozen for possible transfer in the future. Embryos that are predicted to be affected by the disease will not be transferred and will be sent to the WFUHS Clinical Molecular Genetics Laboratory to confirm the previous abnormal results. These embryos will be discarded after confirmational testing. It is possible that no unaffected embryos will be detected and consequently no embryos will be eligible for transfer to the womb. It is also possible that single-gene PGD testing may fail to yield any results. The patient will then have the choice of whether or not to transfer embryos for which no results were obtained with the understanding that such embryos have the same probability of being affected by inherited disease as naturally conceived embryos.

At present, single-gene PGD testing detects about 95% of those embryos carrying a known alteration. This means that approximately 5% of the embryos analyzed have a chance of being misdiagnosed. Consequently, it is strongly advised that patients who become pregnant following single-gene PGD analysis also undergo standard prenatal diagnosis testing, such as CVS or amniocentesis. It is recommended that patients having single-gene PGD testing performed at the WFUHS Clinical Molecular Genetics Laboratory send any prenatal sample for genetic testing to the same laboratory to insure the reliability of the genetic testing. This will confirm that the single-gene PGD analysis was accurate and insure that the fetus is free from the genetic alteration(s) for which the embryo(s) was analyzed. If no prenatal testing is performed, the risk for having an affected child with the disease being analyzed remains at 5% which only accounts for a misdiagnosis due to the single-gene PGD analysis.

Risks

Some studies have shown that congenital abnormalities, birth defects, genetic abnormalities, mental retardation, and/or other possible differences may occur in children born following in vitro fertilization, cell biopsy, and PGD testing. However, these problems also occur in 3-5% of children resulting from natural conception without PGD testing. Single-gene PGD testing may also fail to properly predict whether the offspring will have the specific disease-causing alteration(s). If confirmatory prenatal testing is not performed, it is possible for the offspring to have the disease in question.

Benefits

Single-gene PGD testing can reduce the chances of having a child affected with a specific genetic disease. However, avoidance of genetic disease in any fetus can not be assured as a result of this PGD testing.

Alternatives

Alternatives to having single-gene PGD testing include using donor gametes for IVF procedure, having only a standard prenatal test such as CVS or amniocentesis, or not having any genetic testing performed during the pregnancy.