



# Consent for Preimplantation Genetic Diagnosis (PGD) for Single Gene Disorders

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Print Patient's Name

Date

## Purpose & background

Currently, the only way to determine whether or not an embryo is affected by a genetic disorder is to wait until pregnancy is established and then perform a prenatal test, such as chronic villus sampling (CVS) or amniocentesis. 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 an inherited disorder is present in the developing fetus. If a disorder is detected, parents face the difficult choice of whether to continue or terminate the pregnancy.

The purpose of preimplantation genetic diagnosis (PGD) is to identify affected embryos at a very early stage and avoid transferring them, thus preventing them from implanting in the womb. The effect of such a procedure is to increase the probability that embryos that implant and create a pregnancy will be unaffected by the specific disease tested.

Preimplantation analysis is not yet considered to be a standard technique and consequently we strongly recommend that patients who become pregnant undergo prenatal testing using CVS or amniocentesis. Prenatal testing will reveal whether the preimplantation genetic analysis was correct, and confirm whether or not the fetus has been affected by the genetic disease tested.

## Procedure

The procedure consists of five different steps, usually performed by different experts and laboratories. (i) The first part is in vitro Fertilization (IVF) to create embryos. (ii) The second part is embryo biopsy to remove one cell of the embryo for analysis. (iii) The processing of the cell and (iv) the analysis of the cell is performed by an outside reference laboratory. (v) The final step, the transfer of the embryos to the female patient, is done by Dr. Miller.

## **Abstinence from intercourse**

It is critical that Patients refrain from sexual intercourse for a period of time beginning fifteen (15) days prior to the date that the Patient's eggs are retrieved, and ending not before the date the Patient receives conclusive results of a pregnancy test performed by the Patient's physician. Abstinence from intercourse is required because sperm can survive up to fifteen (15) days in vivo. As such, it is possible that sperm from intercourse may result in fertilization and implantation of an embryo, in addition to, or instead of, fertilization and implantation that results from IVF. This would negate the results of PGD testing.

## **Biopsy of blastomeres**

Patients having PGD first undergo ovarian stimulation and in vitro fertilization, which usually results in the production of several embryos. When the embryos are approximately three days old, a single cell (blastomere) is removed from each of them (provided that they have at least 5 cells - embryos with fewer cells may not be biopsied).

To test the blastomere, the embryologist makes an opening in the covering of the embryo on the third day of development, and aspirates a blastomere with a pipette. The embryo is returned to an incubator, and the cell is placed in a tube and sent to a reference laboratory for analysis. Please read and sign the consent form for embryo biopsy and fixation given to you by Dr. Miller, which will explain the risks of this procedure.

## **Cell transport**

After the cells have been biopsied, washed and placed in a small test tube, the embryologist sends them to a reference laboratory for analysis using same-day or next-morning delivery couriers.

## **Analysis**

The biopsied cells are analyzed by the reference laboratory for the presence of specific changes in the genetic code that cause disease (mutations). Initially, the amount of DNA within the cell is too tiny to be detected and for this reason the DNA must be "amplified". DNA amplification is accomplished using a technique called PCR (polymerase chain reaction). Once the DNA has been amplified to a sufficient level, it may be tested to see if it contains the disease-causing mutation. Mutation testing may involve any one of several different methods.

If the cell is found to be free of the disorder, then it is inferred that the embryo it was derived from is also clear of the disease. Embryos found to be unaffected are transferred to the mother or frozen for transfer in the future. Embryos that are predicted to be affected by the disease will not be transferred.



## Limitations

Several embryos are generated during PGD to maximize the probability that at least one unaffected embryo will be found. However, it is possible that no unaffected embryos will be detected and consequently no embryos will be eligible for transfer to the womb. Additionally, embryos may be excluded from transfer because they are not developing normally.

At present, preimplantation analysis detects about 95% of affected embryos. This means that misdiagnoses can occur, although they are uncommon. The probability of becoming pregnant with an affected fetus is much less after preimplantation testing than it is after natural conception. For patients at risk of passing on a dominant disorder to their children, natural conception usually carries a 1 in 2 chance that the fetus will be affected by the disease. Couples where both parents are carriers of a recessive disorder generally face a 1 in 4 risk of having an affected child.

Currently, other PGD tests, such as those for advanced maternal age to prevent Down syndrome and other chromosome abnormalities, cannot be simultaneously provided with a PGD test for gene disorders.

The preimplantation genetic diagnosis that we perform for you will only provide information concerning the specific mutation(s) that we are made aware of via medical records. Additional genetic disease mutations that might exist in an embryo will not be tested unless specifically requested by the patient and/or care provider and agreed to in writing with the reference laboratory prior to IVF with a PGD cycle.

Mutation to be diagnosed and name of disorder \_\_\_\_\_

## Risks

### The risk of embryo biopsy

If an embryo is damaged by the procedure it will stop growing and will not be suitable for transfer into the uterus. The risk of damaging an embryo during removal of the cell(s) is less than 1%. The future fetus will be complete even if one or two cells are removed from the embryo.

More than 2000 babies have been born from IVF with PGD with no reported increase of congenital abnormalities above the general population rate (the rate of malformations in the general population is 3-5%). However, there have not yet been sufficient PGD cases performed to rule out any detrimental effect on embryo development. Thus, it is still strongly recommended that you have chorionic villus sampling or an amniocentesis

performed, as well as a routine ultrasound examination. IVF with PGD does not guarantee the birth of a normal baby.

## **The risk of cell preparation**

After embryo biopsy, the biopsied cell is placed inside a tiny test tube and then burst, allowing the DNA to be released. After this process, the cells are no longer alive and can only be used for analysis. Not all cells can be analyzed after transfer to the test tube. A small fraction of cells burst before they have been transferred to the test tube or are lost because of technical reasons beyond the control of the individual performing the preparation.

Additionally, some cells do not have a nucleus and contain no analyzable DNA. Such cells will not yield a result. Less than 5% of embryos have cells that cannot be analyzed because they lack a nucleus. A further 3% of embryos cannot be analyzed for other technical reasons. Embryos without analysis can still be transferred, but all the possible advantages of PGD will then not apply.

## **The risk of transport**

Once the cells are fixed a third party transports the cells to the reference laboratory for analysis using same day or next morning delivery services. Weather and air travel conditions may delay the receipt of samples. Rarely samples do not arrive in the reference laboratory or are damaged during transport.

## **The risk of the PGD analysis**

The risk of a clinical misdiagnosis resulting in a fetus or baby affected for the disease that was assessed using PGD varies depending on the disease diagnosed, but is generally <5%. A more precise estimate of misdiagnosis is usually available after the PGD protocol has been tailored to the needs of the individual patient and preliminary testing has been completed.

PGD laboratories may have different misdiagnosis rates. Due to the chance of misdiagnosis, as well as the presence of other genetic abnormalities for which we do not test (for example the risk of Down syndrome for mothers over 35), we recommend prenatal testing by CVS or amniocentesis. CVS and amniocentesis offer higher accuracy and lower misdiagnosis rates than PGD because there are many more cells available for testing with more time available for the testing.

The fetus should also be monitored with ultrasound examination to check its growth and development. There is no guarantee that a child will be normal after IVF with PGD. If most of the embryos tested are found to be abnormal, there may only be a few embryos



suitable for transfer, and none left for freezing. It is possible that none of the embryos will be found to be normal, and, in this case, embryo transfer will not be performed.

Due to technical problems, or because the cell chosen for biopsy lacked a nucleus, about 10% of embryos will not have a diagnosis. Embryos without analysis can still be transferred, but all the possible advantages of PGD will not apply.

It is essential that the cell biopsied from an embryo is the only source of DNA analyzed. If any other cells or DNA enter the test tube containing the biopsied cell, then the results of the analysis will be unreliable. We make a great effort to ensure that contamination of the sample with extra cells or DNA does not occur. However, even the most careful procedures cannot entirely eliminate this possibility. Contamination usually affects less than 5% of cells tested during PGD. The reference laboratory will perform a number of additional tests to assess whether or not contamination is present in each sample, allowing most cases of contamination to be detected. If a cell is affected by contamination, the embryo from which it is derived cannot be recommended for transfer.

## Benefits

A benefit of PGD includes improving the chances of avoiding a specific genetic disease in the fetus thus reducing the chance that you will have to face a decision concerning pregnancy termination. However, neither becoming pregnant nor avoidance of a genetic disease or chromosomal abnormality in any fetus or offspring can be assured as a result of these procedures. No guarantee is made regarding the outcome of PGD

## Alternatives

Alternatives to preimplantation genetic diagnosis include standard prenatal testing for abnormalities during pregnancy (chorionic villus sampling, amniocentesis, ultrasound examination). You are not obliged to undergo PGD even if your physician recommends it.

You should undergo recommended prenatal testing that is based on your age and medical history. The risks, benefits and alternatives of this testing should be discussed thoroughly with your genetic counselor, obstetrician or the person performing/ordering the tests. If you wish to be referred to a genetic counselor in your area, please inform us. Although these tests may serve as alternatives to PGD, PGD is not a substitute for prenatal testing.

You are strongly recommended to seek prenatal diagnosis if you become pregnant. Prenatal testing using first trimester CVS or second trimester amniocentesis can confirm whether or not the preimplantation genetic analysis was accurate and reveals whether the fetus is free from the genetic abnormalities for which the embryo was tested. Refusal to undergo CVS or amniocentesis may leave you in the same position as if you had conceived a child naturally, with the same risks of producing a child who has a genetic or

chromosome abnormality.

## Confidentiality

Confidentiality of your records will be maintained in accordance with applicable state and federal laws at all times.

## Genetic consultation before PGD

It is recommended that you have a consultation with a genetic counselor that specializes in PGD before undergoing PGD. This can be arranged through Women's Fertility Center [Subject to state law requirements].

## Specimen retention

The cells to be tested will be destroyed during the process of the analysis. This will usually occur within 5 days of the biopsy. The cells to be tested will be destroyed during the process of the analysis. This will usually occur within 5 days of the biopsy. After testing has occurred, the reference laboratory will retain blood, chromosomes and/or the DNA until three months after the birth of the baby; the specimen is retained for follow up and preparation of future cycles.

## **Informing investigators regarding health of offspring**

A pregnancy can be tested via chorionic villous sampling (CVS) or amniocentesis. Your obstetrician, or someone he or she refers you to, can perform these tests locally. If prenatal diagnostic testing is not performed, genetic analyses should be performed on cord blood at the time of delivery.

If a pregnancy loss occurs, we request that genetic studies be performed on the products of conception. We request that all results from genetic testing of the pregnancy or the child up to the age of one year be forwarded to the PGD Program Coordinator at the reference laboratory. This information will remain confidential and will be used to monitor outcomes of the PGD program.

## Costs

Fees for PGD are in addition to the cost of the IVF cycle. The Finance Department of Women's Fertility Center will advise you of the fees. If the PGD procedure is paid for but not performed, your payment will be refunded less the cancellation fee.

You are also responsible for any additional medical costs incurred as a result of complications or other medical care required as a result of receiving PGD. Insurance cover for all or any part of this total procedure may not be available, and you are personally responsible for payment of such costs, including hospital and laboratory



charges, and the physician's professional fees.

## Declaration

We hereby confirm that we have read the entire consent form, or that it has been read to us, and that we understand it completely. We further confirm that we have been given an opportunity to ask questions about the PGD procedure and the contents of this consent form, and that any and all questions of mine/ours regarding this form or this study have been answered to my/our complete satisfaction. We understand that PGD has benefits and risks, some of which may be unknown at this time. We also understand that PGD may fail to yield a result and that misdiagnosis is possible. We wish to proceed with PGD for the single gene disorder stated above.

We understand that undergoing PGD does not eliminate the need for standard prenatal testing such as chorionic villous sampling or amniocentesis. The need for these tests remains the same whether or not PGD is performed. We understand that if we have questions about CVS or amniocentesis we may ask our obstetrician or we may request a referral to a genetic counselor.

If we think of additional questions, we may contact our physician, genetic counselor or nurse.

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Patient's Signature

Date

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Partner's Signature

(if not applicable, write NA)

Date

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Witness Signature

Print name

Date

You may request a copy of this form for your records.

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Signature of Nora Miller, MD

Date