FAMILY FERTILITY CENTER **www.familyfertility.com**
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Consent to Embryo Biopsy for
Pre-implantation Genetic Screening (PGS)

I. BACKGROUND

A. Abnormal number of chromosomes or Aneuploidy

Chromosomes are structures found in the center or nucleus of cells. A human typically has 46 or 23 pairs of chromosome. An embryo receives 23 chromosomes from the sperm and 23 from the egg. Chromosomes are made of genes, which contain the information that instructs the body how to function. An embryo with extra or missing chromosome(s) (called aneuploidy) is the most common cause of miscarriage as well as failure to have a successful pregnancy with in-vitro fertilization.

B. Pre-implantation genetic screening (PGS)

Pre-implantation genetic screening (PGS) of human embryo is to analyze each embryo for aneuploidy. There are several laboratory techniques used in PGS. Currently, the most widely used methods for human embryos involve screening all 24 chromosomes in an embryo and is coined comprehensive chromosomal screening (CCS). Molecular genetic testing methodologies are rapidly evolving. It is beyond the scope of this consent form to describe each and every method. Please refer to the particular testing laboratory website for more information on this topic. This consent form specifically addresses the biopsy procedure on an embryo before PGS with CCS can be performed.

II. PURPOSE OF PGS

The purpose of PGS is to identify, select and transfer into the uterus only embryo(s) that do not have recognizable chromosomal abnormalities. Transfer of an embryo with normal PGS result increases the likelihood of successful pregnancy outcome, decreases the risk of miscarriage, and allows an elective single embryo transfer. PGS may also be used for patients of all ages who have unexplained failure to conceive despite several IVF cycles. Other patients who may benefit are patients with a history of miscarriages, especially when testing reveals no clear explanation. Patients who have had an aneuploid pregnancy in the past may also want to consider PGS

III. PROCEDURE

The entire process of pre-implantation genetic screening (PGS) consists of six different steps, usually performed by different experts and laboratories.

(i) The first part is in-vitro fertilization (IVF) with either conventional IVF or intracytoplasmic sperm injection (ICSI) by which embryos are produced. This part occurs at Family Fertility Center.

(ii) The second part is embryo biopsy. Embryo biopsy can be performed at either Day 3 of embryo development (blastomere biopsy) or Day 5/6 of development (trophectoderm biopsy).
(a) In Day 3 embryo biopsy, typically one (sometimes two) cell is removed to be analyzed.
(b) In Day 5/6 embryo biopsy, several (3 to 6) cells are removed to be analyzed.

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Embryo biopsy is done at the Family Fertility Center by our own staff or outside experts who perform embryo biopsy frequently.

See Sections III. A and III. B below for details on embryo biopsy.

(iii) After the cells are biopsied and placed in test tubes, the tubes are transported by same-day overnight courier to outside reference laboratory for analysis.

(iv) The analysis of the cell is performed by an outside reference laboratory. Currently Family Fertility Center sends its PGS specimens to the following reference laboratories:
(a) Reprogenetics (www.reprogenetics.com) in West Orange, New Jersey,
(b) Genesis Genetics (www.genesisgentics.org) in Plymouth, Michigan,
(c) Reproductive Genetics Institute (www.reproductivegenetics.com) in Chicago, Illinois,
(d) CombiMatrix (www.combimatrix.com) in Irvine, California,
(e) Other _____, or
(f) a reference laboratory as dictated by insurance plan.

(Dr. H Christina Lee and the Family Fertility Center have no financial interest in and receive no incentive, bonus or payment from any genetic testing laboratory)

There are several testing methods to analyze or screen all 24 chromosomes, also called comprehensive techniques (CCS). Currently the most common methods for CCS are:
a. Array-Comparative Genomic Hybridization or aCGH, although a newer method
b. Next-Generation Sequencing or NGS is on the horizon.

Both methods are performed on several cells from a day 5 or day 6 embryo, or less commonly on one or two cells from a day 3 embryo.

(v) Comprehensive chromosomal screening (CCS) often requires over 24 hours before the result is available. Hence freezing of the embryos using vitrification method with a subsequent frozen embryo transfer are often necessary. For details on freezing of human embryos and frozen embryo transfer, please consult the corresponding consent forms. Freezing of the embryos takes place at Family Fertility Center.

(vi) The final step, the thawing of frozen embryos and the transfer of embryos into the female patient, is done by physician(s) at Family Fertility Center.

A. Biopsy of a day 3 embryo

There are three steps to remove one to two cells from a day 3 embryo. Generally only embryos with six (6) or more cells are biopsied. In the first step, the embryo is immersed in a solution with no calcium and magnesium. This loosens the cell-to-cell connection in the embryo, permitting the removal of one or two cells. Then a microscopic opening is made in the covering of the embryo (hatching), usually with laser beam. Immediately after the opening is made, one to two cells from the embryo is removed with a small

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pipette using gentle aspiration. The embryo is returned to an incubator after the biopsy.

B. Biopsy of a day 5 or day 6 embryo

There are two steps to remove a few cells from a day 5/6 embryo, but the two steps are usually done on separate days. In the first step, a microscopic opening is made in the covering of the embryo (hatching) between the third to the fifth/sixth day of embryonic development, generally with a laser beam.

The second step is done on the fifth or sixth day of development. It involves the aspiration of a few (3-6) cells from the embryo with a pipette and removal of the cells by cutting it with laser beam. The embryo is returned to an incubator after the biopsy.

C. TRANSPORT OF SPECIMENS

After the cells have been biopsied, the cells are placed inside test tubes. The tubes are transported by same-day overnight courier to outside reference laboratory for analysis.

D. ANALYSIS OF THE BLASTOMERES OR TROPHECTODERM CELLS

Before testing can be done on the cells biopsied from an embryo, whether day 3 or day 5, the genetic material (DNA) of the embryonic cells is amplified using a technique called polymerase chain reaction. (PCR). This amplification produces enough DNA material so the actual testing can be performed.

The amplified genetic material is then tested for aneuploidy using array comparative genomic hybridization (aCGH) or a newer method next generation sequencing (NGS). It is likely that NGS will soon replace aCGH altogether. Both aCGH and NGS determine the amount of DNA derived from each chromosome, revealing whether or not there are a correct number of chromosomes. NGS detects substantially more markers on each chromosome, making it more reliable than aCGH. Either analysis generally requires twenty-four or more hours to complete.

IV. LIMITATIONS OF TEST METHODS

PGS does not guarantee the birth of a normal baby. Every method of PGS has inherent limitations. For example: both aCGH and NGS are techniques to detect the number variations in whole chromosomes but neither method can detect structural re-arrangement (such as translocation or inversion) or sub-chromosomal variations. While NGS is more sensitive than aCGH to detect abnormal copy number of the entire set of chromosome, called triploid or tetraploid, neither technique can detect all levels of mosaicism. Mosaic embryos that have similar amounts of monosomic and trisomic cells may produce a "normal" result. Furthermore many birth defects, mental retardation, medical diseases and predisposition to diseases or cancer have no known or identifiable genetic basis or their genetic basis is not related to the DNA gene sequence.

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Although biopsy of embryos with PGS has been performed worldwide for over 15 years, the experience with this technique is still somewhat limited, and it is therefore considered investigational in many centers.

Because of these limits, prenatal genetic testing after the IVF cycle with PGS is strongly advised in order to confirm the diagnosis and review the number and structure of all the chromosomes. Prenatal testing may be done in the first trimester via chorionic villus sampling (CVS) or during the second trimester via amniocentesis. CVS is a procedure done in the late first trimester that takes cells from the placenta and analyzes them for chromosomal abnormalities. Amniocentesis is a procedure usually done between 15 and 20 weeks of pregnancy that takes fluid from around the baby and analyzes the baby's cells in the fluid for chromosomal abnormalities. PGS should not be considered a replacement for prenatal genetic testing, as its accuracy rate is not as high. The gender given for individual embryos is an estimate only and should not be considered diagnostic. Alternative methods during pregnancy may provide more accurate information concerning the gender of any fetuses resulting from these procedures.

V. RISKS OF PGS

A. Risk of embryo biopsy

Hatching or making an opening in the zona pellucida, or shell around the embryo, does not appear to inhibit embryo development and implantation. No part of the fetus will be lacking because one or few cells are removed from a day 3 or day 5/6 embryo. The procedure may delay development by a few hours, but likely will continue its normal development. This has been observed thousands of times in humans and other animals after embryo freezing, when one or more cells normally fail to survive the thaw. Limited studies show that embryo biopsy on day 3 may possibly reduce the chance of embryo survival after freezing or vitrification.

As of 2011, more than a thousand babies have been born world wide from IVF with PGS with no reported increase of congenital abnormalities above the general population rate. The rate of malformations in the general population is 3-5%. This procedure, however, has not been performed enough yet to rule out any detrimental effect. Thus it is still strongly recommended that the fetus be monitored with standard obstetric ultrasound examination for structural malformation after PGS.

B. Risk of transporting the specimen

Once the cells are fixed, a third party transports the cells to the reference laboratory for analysis. This is done using same day or next morning delivery services. Weather and air travel conditions may delay the reception of samples. In about 1/1000 cases, samples do not arrive in the reference laboratory. Even more rarely, 1/3000, samples may be damaged during transport.

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C. Risk of the PGS analysis

i. No diagnosis or partial diagnosis

In less than 15% of human embryos biopsied, the embryologists and geneticists are (1) unable to remove the cells to obtain the diagnosis, (2) unable to perform the genetic procedure due to technical problems, (3) obtain inconclusive or uncertain results, or (4) damage the embryo so that it cannot be transferred.

Some embryos will have no diagnosis, due to the loss of biopsied cells, or poor DNA quality (often found in damaged or dying cells). Embryos without a result can still be replaced, but all the possible advantages of PGS will not apply. In addition, sometimes the analysis may not be clear for one of the chromosomes being tested. Again, this embryo could be replaced, but the possible advantages of PGS may not apply.

ii. Misdiagnosis

It is possible that a chromosomally normal embryo may be incorrectly identified as an affected embryo and therefore not replaced into the uterus, or that a chromosomally abnormal embryo is incorrectly identified as a normal embryo and transferred into the uterus. There is also a possibility that embryo biopsy could accidentally destroy the embryo and that this damage could affect the future development of the fetus. It is not possible to guarantee that a pregnancy will occur with uterine placement of embryos that have been chromosomally screened or diagnosed for the absence of mutations. In addition, a miscarriage can occur after a woman becomes pregnant through IVF.

The risk of a clinical misdiagnosis, that is, the occurrence of a fetus or baby with chromosome abnormalities after a PGS procedure, varies between less than 1% to 3% depending on the specific laboratory and methodology. Please consult with the specific testing laboratory about its clinical misdiagnosis rate. Overall the risk of misdiagnosis is lower than the rate of aneuploidy without PGS or in natural conceptions especially in women of advanced maternal age.

Due to the chance of misdiagnosis, as well as the presence of aneuploidy involving extra copy set of entire set of chromosome (e.g. triploid or tetraploid), mosaicism or chromosomal re-arrangement (e.g. inversion or translocation) not detectable by current PGS methods, a pregnancy after PGS must be carefully monitored. Between 10 to 18 weeks, it is strongly recommended that chorionic villus sampling (CVS) or an amniocentesis be performed. CVS and amniocentesis offer higher accuracy and lower misdiagnosis rates than PGS. 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 PGS.

iii. No Normal Embryos

If none of the embryos is tested normal, there may not be an embryo replacement. The likelihood that this will happen is dependent on the age of the female.

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iv. Identical twinning

There is a much greater chance of getting pregnant with identical twinning in IVF patients compared to spontaneous conceptions (1.5 to 2% vs. 0.5%).

VI. POSSIBLE BENEFITS

In most cases, aneuploid embryos are indistinguishable morphologically and developmentally from chromosomally normal ones. Thus, without genetically testing them, aneuploid embryos may be transferred. Most chromosomally abnormal embryos either do not implant or spontaneously abort shortly after implantation.

Genetic testing of the preimplantation embryo can determine whether the embryo could potentially be affected by a chromosomal abnormality. Therefore the chance of conceiving a baby with a chromosomally abnormality will be reduced by more than 90% after PGS. However, as described in Section V.A. and Section V.C. ii. , prenatal genetic diagnosis after conceiving with PGS is strongly recommended in order to confirm that the PGS results were accurate.

VII. ALTERNATIVES

Alternatives to PGS include standard prenatal testing for abnormalities after a pregnancy is established. This includes chorionic villous sampling (CVS), amniocentesis, and ultrasound examination of the fetus.

PGS does not screen for all forms of chromosomal abnormalities, genetic mutation or birth defect. Prenatal testing must be done after a pregnancy is established even if the PGS results were normal.

The risks, benefits and alternatives to PGS should be discussed thoroughly with a genetic counselor, obstetrician or the person performing/ordering the tests before consent to PGS. If counseling with a genetic counselor is desired, please ask for references.

VIII. COSTS

Fees for PGS are in addition to the cost of the IVF cycle. There are charges for the biopsy, as well as the actual PGS on the embryonic cells. Please consult with the finance staff at the Family Fertility Center regarding the cost for the different components of this procedure. Also refer to the brochure from the testing reference lab regarding the cost of different PGS panels. If the PGS procedure is paid for but not performed, payment may be refunded as dictated by the policy of the specific testing reference laboratory. Any incidental or consequential cost incurred as a result of complications or other medical care required as a result of receiving PGS is not included in the charges for PGS. Insurance coverage for all or any part of this total procedure may not be available

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IX. CONFIDENTIALITY

Both federal law, Health Insurance Portability and Accountability Act (HIPAA), and state law require confidentiality of all medical records be maintained at all times. Only personnel of the testing reference laboratory and Family Fertility Center who participates in the procedure will have access to the medical records to the extent allowed by law. Also the Department of Health in Pennsylvania and the Food and Drug Administration (FDA) may inspect the records.

X. GENETIC CONSULTATION BEFORE PGS

It is highly recommended to have a consultation with a board certified genetic counselor specialized in PGS before undergoing PGS. References can be obtained from the Family Fertility Center, or consultation may be made directly with a genetic counselor at the testing reference laboratory.

XI. 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. In case the test was not performed for any unusual reason, the sample will be destroyed within 60 days of reception, as stipulated by policy of specific testing reference laboratory.

XII. FOLLOW-UP

Testing of a pregnancy after PGS can be done via CVS or amniocentesis. If prenatal diagnostic testing is not performed, chromosome analyses should be performed on cord blood at the time of delivery. If a pregnancy loss occurs, it is strongly recommended that chromosome studies be performed on the loss. Please forward all results from genetic testing of the pregnancy or the child up to the age of one year to the PGS Program Coordinator at the testing reference laboratory. This information will remain confidential and will be used to monitor outcomes of the PGS program at the testing reference laboratory.

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XIII. ACKNOWLEDGEMENT

We have read the entire consent form, or it has been read to us. We understand that PGS has benefits and risks, some of which may be unknown at this time. We want to proceed with PGS for aneuploidy.

We also understand that undergoing PGS for aneuploidy does not eliminate the need for standard prenatal testing such as CVS or amniocentesis. The need for these tests remains the same whether or not PGS for aneuploidy 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.

We have been given an opportunity to ask questions about the PGS procedure and the contents of this consent form. This consent form is freely and voluntarily executed by us. We have not relied on any inducements, promises, or representations made by Dr. H. Christina Lee, the Family Fertility Center or its staff.

_____

Print Name of Spouse or Partner Signature Date

_____

Print Name of Spouse or Partner Signature Date

_____

Print Name of Witness Signature Date

_____

Ha-Lin Christina Lee, M.D., J.D., H.C.L.D. Date