FAMILY FERTILITY CENTER **www.familyfertility.com**
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CONSENT TO EMBRYO BIOPSY FOR PREIMPLANTATION GENETIC TESTING

I. BACKGROUND

A. Pre-implantation genetic testing (PGT)

Pre-implantation genetic testing historically is divided into pre-implantation genetic screening (PGS) or pre-implantation genetic diagnosis (PGD). In 2017 the International Glossary on Infertility and Fertility Care revised the terminology. The new name for all tests is Preimplantation Genetic Testing (PGT). This includes:

* PGT for aneuploidy (PGT-A) - previously PGS
* PGT for single gene mutation (PGT-M)- previously PGD
* PGT for chromosomal structural rearrangements (PGT-SR) – previously PGS translocation

B. Pre-implantation genetic testing for aneuploidy (PGT-A)

Chromosomes are structures found in the center, or nucleus, of cells. A human typically has 46 (or 23 pairs) of chromosomes. An embryo typically 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.

PGT-A of a human embryo will analyze an embryo for the number and identity of chromosomes or screen for aneuploidy. Currently, the most widely adopted commercially available methods for PGT-A on human embryos involve screening all 24 chromosomes in an embryo and is coined comprehensive chromosomal screening (CCS). There are several molecular techniques used in CCS, e.g. array comprehensive genomic hybridization (CGH), single nucleotide polymorphism microarray (SNP Microarray), next generation sequencing (NGS), and quantitative polymerase chain reaction (qPCR). 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 or consult with its genetic counselor for more information on this topic.

C. Pre-implantation genetic testing for single gene mutation (PGT-M) or chromosomal rearrangement (PGT-SR)

PGT-M of a human embryo will diagnose whether an embryo inherits one or more copies of a known genetic mutation from one or both of the parents, or from person(s) contributing the gamete(s) (sperm and egg). Before PGT-M can be performed on a human embryo, the nature of the genetic mutation carried by the person(s) contributing the gamete(s) must be identified. Usually a genetic probe specifically made to identify the mutation must be manufactured and tested. In the alternative, the location of the mutation can be deduced based on the DNA sequence of the neighboring genes, a method called linkage analysis. It is beyond the scope of this consent form to describe the complexity of molecular genetic testing. Please refer to the particular testing laboratory website or consult with its genetic counselor for more information on this topic.

PGT-SR of a human embryo will diagnose whether an embryo inherits an abnormal set of re-arranged (translocated or inverted) chromosome, usually from one of the parent with a balanced translocation of chromosome. Similar to PGT-M, in PGT-SR a genetic probe specifically made to identify the re-arranged

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chromosomal segment must be manufactured and tested prior to any embryo being created with assisted reproductive treatment.

This consent form specifically addresses the biopsy procedure on an embryo before PGT-A with CCS, PGT-M, or PGT-SR is performed.

Please refer to the particular testing laboratory website or consult with its genetic counselor for more information on the specifics of PGT-A, PGT-M and PGT-SR.

II. PURPOSE OF PREIMPLANTATION GENETIC TESTING

A. Preimplantation genetic testing for aneuploidy (PGT-A)

The purpose of PGT-A 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 PGT-A result increases the likelihood of successful pregnancy outcome, decreases the risk of miscarriage, and allows an elective single embryo transfer. PGT-A 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 PGT-A.

B. Preimplantation genetic testing for single gene mutation (PGT-M) or rearranged chromosome (PGT-SR)

The purpose of PGT-M is to identify, select and transfer into the uterus only embryo(s) that do not have the known genetic mutation carried in one or both of the parent(s) or person(s) contributing the gametes. The genetic mutation being tested for in PGT-M is usually known to cause severely impaired cellular function(s) leading to chronic debilitating illness and/or premature death. Such genetic mutation can be recessive, requiring two copies (one from the egg, one from the sperm) of a genetic mutation for the clinical disease to be manifested. Or the genetic mutation can be dominant, requiring just one copy (from either the egg or sperm) of a genetic mutation for the clinical disease to be present. Transfer of an embryo with normal PGT-M result increases the likelihood of successful pregnancy outcome, minimizing the possibility of having a chronic debilitating or life-threatening disease.

The purpose of PGT-SR is to identify, select and transfer into the uterus only embryo(s) that do not have the known chromosomal rearrangement carried in usually one of the parents or persons contributing the gametes. The chromosomal rearrangement being tested for in PGT-SR is usually the cause for recurrent pregnancy losses or occasionally severely impaired cellular function(s) leading to chronic debilitating illness and/or premature death.

PGT-M or PGT-SR is performed only on an embryo biopsy specimen tested **euploid** by PGT-A. As such PGT-M or PGT-SR is never performed on an embryo biopsy specimen without first undergoing PGT-A. PGT-M or PGT-SR is an additional genetic test after PGT-A is performed on an embryo biopsy.

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III. PROCEDURE

The entire process of pre-implantation genetic testing (PGT) 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 or 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 (5 to 8) cells are removed to be analyzed.

Currently only day 5 or 6 embryo biopsy is performed in most clinics as day 3 embryo biopsy has been shown to be deleterious to the development of the embryo.

Embryo biopsy is done at the Family Fertility Center by our own staff.
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 courier to outside reference laboratory for analysis.

(iv) The analysis of the cells is performed by an outside reference laboratory. Currently Family Fertility Center sends its PGT 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) Igenomix (www.igenomix.com) Jersey City, New Jersey, or
(d) 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)

(1) PGT-A
There are several testing methods to analyze or screen all 24 chromosomes, also called comprehensive chromosomal screening (CCS), in PGT-A. Currently the two most common methods for CCS are:
- Array-Comparative Genomic Hybridization or aCGH, or
- Next-Generation Sequencing or NGS.

All methods of PGT-A 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.

(2) PGT-M and PGT-SR
When PGT-M or PGT-SR is indicated, only those embryo biopsy specimens tested euploid by the PGT-A will undergo additional testing for PGT-M or PGT-SR on the same specimen in a subsequent and separate genetic test.

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(v) Comprehensive chromosomal screening (CCS) often requires over 24 hours before the result is available. Additional time to undergo PGT-M or PGT-SR. Hence freezing of the embryos using vitrification method with a subsequent frozen embryo transfer are 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 or 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 pipette using gentle aspiration. The embryo is returned to an incubator after the biopsy.
Family Fertility Center performs biopsy on a day 5-6 embryo exclusively, as is the case in most clinics. Day 3 embryo biopsy has been shown to be deleterious to the development of the embryo and is no longer performed by most clinics.

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 or sixth day of embryonic development, generally with a laser beam.

The second step is done on the fifth or sixth day of embryo development. It involves the aspiration of a few (5-8) cells from the embryo with a microscopic 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 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 or 6, 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 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 PREIMPLANTATION GENETIC TESTING

A. Testing of limited materials

PGT should not be considered a replacement for prenatal genetic testing, as its accuracy is limited by testing only a few cells removed from an embryo.

B. Limitation of test method

No genetic testing can guarantee the birth of a normal baby. Every method of genetic testing has inherent limitations. IN PGT-A, 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 chromosomes, 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.

Likewise, PGT-M or PGT-SR is about 98% accurate but is still considered a screening tool. Hence prenatal genetic testing with CVS or amniocentesis is recommended in spite of normal PGT-M or PGT-SR test result.

Because of these limits, prenatal genetic testing after the IVF cycle with PGT is strongly advised in order to confirm the diagnosis. Prenatal testing may be done in the first trimester with non-invasive prenatal testing (NIPT) or invasive testing in the late first or second trimester. Examples of NIPT include cell free DNA testing, nuchal translucency measurement, and integrated or sequential prenatal genetic testing with a combination of blood markers and nuchal translucency measurement. NIPT can be performed to confirm results of PGT-A.

Invasive prenatal genetic testing includes chorionic villus sampling (CVS) or amniocentesis. CVS and amniocentesis are recommended in spite of normal results after PGT-M. CVS is a procedure done in the late first trimester that takes cells from the placenta and analyzes them for chromosomal or single gene 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 or single gene abnormalities. CVS and amniocentesis offer higher accuracy and lower misdiagnosis rates than PGT as more cell materials are being tested.

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.

No genetic testing can completely rule out any birth defect or developmental delay. The fetus should also

be monitored with ultrasound examination to check for structural defect, growth and development.

V. RISKS OF PREIMPLANTATION GENETIC TESTING (PGT)

A. Risk of embryo biopsy

i. Assisted hatching of the embryo

Assisted hatching, or making an opening in the zona pellucida, or shell around the embryo, is necessary before a biopsy can be performed on an embryo, regardless of whether it is a day 3 or day 5-6 embryo. Available data on assisted hatching does not reveal any negative impact on embryo development and implantation.

ii. Embryo biopsy

The actual removal of a small number of cells from an embryo can at least theoretically in some way harm the embryo, consequentially impair the growth of the embryo or even future development of the resulting fetus. Studies on day 3 embryo biopsy supported the notion that the biopsy procedure on such an early stage embryo reduced the chance of pregnancy and live birth. On the other hand, studies on day 5-6 embryo biopsy are more reassuring. Embryo biopsy on a day 5-6 embryo has no demonstrable deleterious impact on the chance of pregnancy and live birth.

As of 2018, many thousand babies have been born world wide from IVF with PGT, with no reported increase of congenital abnormalities above the general population rate. The rate of malformations in the general population is 3-5%. Still, because this procedure has not been performed long enough to completely rule out any detrimental effect, it is strongly recommended that the fetus be monitored with standard obstetric ultrasound examination for structural malformation after embryo biopsy for PGT.

B. Risk of transporting the specimen

Once the cells are removed from an embryo, 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.

C. Risk of the genetic analysis

i. No diagnosis or partial diagnosis

In up to 15% of human embryos biopsied, no diagnosis, inconclusive or uncertain results may be obtained. This is usually due to (1) insufficient number of cells were biopsied, (2) the biopsied cells had poor DNA quality (often found in damaged or dying cells, or (3) the biopsied cells are lost. Embryos without a result can still be transferred into the uterus, but all the possible advantages of PGT will not apply.

ii. Misdiagnosis

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It is possible that a chromosomally or genetically normal embryo may be incorrectly identified by PGT as an affected embryo and therefore not transferred into the uterus. Conversely, a chromosomally or genetically abnormal embryo can be incorrectly identified by PGT as a normal embryo and transferred into the uterus.

The risk of a clinical misdiagnosis, that is, the occurrence of a fetus or baby with chromosome or genetic abnormalities after PGT varies between less than 1% to 3% depending on the specific laboratory, methodology, and nature of the genetic mutation. Please consult with the specific testing laboratory about its clinical misdiagnosis rate. Overall the risk of misdiagnosis is lower than that in natural conception without PGT.

Because of the possibility of misdiagnosis in PGT, and the inability of current methods to detect the presence of aneuploidy involving extra set of chromosomes (e.g. triploid or tetraploid), mosaicism, or chromosomal re-arrangement (e.g. inversion or translocation), a pregnancy after PGT must be carefully monitored as described in Section IV: LIMITATIONS OF TEST METHODS. The fetus should also be monitored with ultrasound examination to check for structural defect, growth and development.

iii. No normal embryos

If none of the embryos test normal, there may not be an embryo transfer. The likelihood that this will happen is dependent on the age of the female and the number of embryos obtained.

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%).

v. No Guarantee of Pregnancy, Live Birth or a Healthy Child

In spite of transferring an embryo or embryo(s) that were tested euploid, or euploid and free from the targeted single gene mutation after IVF and PGT, there is no guarantee that a pregnancy will occur. In addition, a miscarriage can still occur after a woman becomes pregnant in spite of such treatment. Similarly, there is no guarantee that a child conceived after these processes will be normal, free from any disease, birth defect, developmental delay, or mental retardation.

VI. POSSIBLE BENEFITS

In most cases, chromosomally or genetically abnormal embryos are indistinguishable morphologically and developmentally from normal ones. Thus, without genetically testing them, aneuploid embryos or genetically abnormal may be transferred. Most chromosomally abnormal embryos either do not implant or spontaneously abort shortly after implantation. Chromosomally normal, euploid embryos, carrying the undesirable genetic mutation can implant and give rise to a child with chronic debilitating illness and/or eventual premature death.

Preimplantation genetic testing can determine whether the embryo could potentially be affected by a

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chromosomal or genetic abnormality. Therefore, the chance of conceiving a baby with a chromosomal and/or genetic abnormality will be reduced by more than 90% after PGT. However, as described in Section IV, prenatal genetic diagnosis after conceiving with PGT is strongly recommended in order to confirm that the PGT results were accurate.

VII. ALTERNATIVES

Alternatives to PGT include standard prenatal testing for abnormalities after a pregnancy is established. This includes non-invasive prenatal testing (NIPT), invasive prenatal testing such as chorionic villous sampling (CVS), or amniocentesis, and ultrasound examination of the fetus.

PGT 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 PGT results were normal.

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

VIII. COSTS

Fees for PGT are in addition to the cost of the IVF cycle. There are charges for the biopsy, as well as the actual PGT testing 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. Refer to the brochure from the testing reference lab regarding the cost of different PGT for aneuploidy panels.

If PGT for single gene mutation, or PGT-M, is to be performed, custom DNA probe for the specific gene mutation must be manufactured and tested before any embryo is to be created with IVF and biopsied. There is additional cost associated with the manufacturing and testing of custom DNA probes.
Because PGT-M is an additional genetic test performed only on an embryo biopsy specimen tested **euploid** by PGT-A, there are two separate charges when PGT-M is indicated, one for PGT-A and one for PGT-M.

Indication(s)	Pre-Procedure Custom Probe	Embryo biopsy	Test(s)	Charges incurred
Screen for aneuploid	No	Yes	PGT-A	Embryo biopsy and PGT-A
Diagnose single gene mutation	Yes	Yes	PGT-A and PGT-M	Custom probe, embryo biopsy, PGT-A and PGT-M
Diagnose chromosomal rearrangement	Yes	Yes	PGT-A and PGT-SR	Custom probe, embryo biopsy, PGT-A and PGT-SR

If the PGT procedure is paid for but not performed for any reason, payment may or may not 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 PGT is not included in the charges for PGT. Insurance coverage for all or any part of this total procedure may not be available.

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 participate 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 PGT

It is strongly recommended to have a consultation with a board certified genetic counselor specialized in PGT **before** undergoing PGT. 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 PGT can be done via NIPT, CVS or amniocentesis. If prenatal diagnostic testing is not performed, chromosomal or genetic analyses should be performed on cord blood at the time of delivery. If a pregnancy loss occurs, it is strongly recommended that chromosomal or genetic 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 PGT Program Coordinator at the testing reference laboratory. This information will remain confidential and will be used to monitor outcomes of the PGT program at the testing reference laboratory.

XIII. ACKNOWLEDGEMENT

We have read the entire consent form, or it has been read to us. We understand that PGT has benefits and risks, some of which may be unknown at this time. We also understand that undergoing PGT for aneuploidy or single gene mutation does not eliminate the need for standard prenatal testing such as NIPT, CVS or amniocentesis. The need for these tests remains the same whether or not PGT is performed. We understand that if we have questions about NIPT, 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 PGT 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.

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We want to proceed with embryo biopsy for (check all that apply, then both partners initial next to the corresponding test)

☐ _____ preimplantation genetic testing for aneuploidy

☐ _____ preimplantation genetic testing for single gene mutation

☐ _____ preimplantation genetic testing for translocation

Indication(s) _____

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_____

_____

_____

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