Informed Consent for Preimplantation Genetic Testing

FM160-1

PURPOSE: The purpose of Preimplantation Genetic Testing (PGT) is to screen embryos created through in vitro fertilization (IVF) for chromosome abnormalities prior to implantation. IVF with PGT allows physicians to transfer embryos predicted to be free of a common chromosome abnormality. Hence, PGT may increase the chance of a successful pregnancy.

There are a total of 46 chromosomes (23 pairs) in each human cell. Half of these chromosomes are inherited from the egg and the other half from the sperm. For normal growth and development, a person must inherit the correct number of chromosomes from each reproductive parent: one each of the 22 autosomes (numbered 1–22) and a sex chromosome (X or Y).

Aneuploidy refers to a type of chromosome abnormality where there are more or fewer than the normal 46 chromosomes present. An aneuploid embryo is an embryo with the wrong number of chromosomes (either too few or too many; or with extra or missing segments of chromosomes). The extra or missing chromosome(s) can come from the egg or the sperm, however, most come from the egg and the chance of aneuploid embryos increases with maternal age. Most aneuploid embryos do not result in a healthy live birth: many lead to spontaneous miscarriage, some fail to implant in the uterus (failed implantation), and some result in a baby with birth defects, intellectual disability and/or other health problems. A common example is an extra copy of chromosome 21; this is called trisomy 21, or Down syndrome.

PROCEDURE: A small sample (a few cells) from each embryo at the blastocyst stage is removed (biopsied) and shipped to Invitae for analysis. All embryos will be frozen and will remain at your IVF center for a future frozen embryo transfer. IVF, embryo biopsy, sample preparation, sample transport, embryo freezing (cryopreservation), and the frozen embryo transfer procedures will take place through your IVF clinic. Only the analysis of the biopsy samples occurs at Invitae. Results from the analyses of these samples is used to infer the chromosomal makeup of the rest of the embryo and resulting pregnancy/child.

Despite special and careful packaging, samples may be damaged or destroyed during shipping. Samples may be delayed because of weather, transportation issues, or other unforeseen reasons beyond the control of Invitae. There is also a chance that the sample received by Invitae is unacceptable for analysis and results cannot be obtained.

Consultation with a genetic counselor or clinical genetics professional (generally referred to as genetic counselor in this document) is available prior to undergoing PGT and signing this consent form. A genetic counselor can review the PGT procedure, including the benefits and limitations of the testing, and answer any additional questions.

METHODS: Testing is performed on biopsied cells (trophectoderm or blastocyst biopsy) received from embryos created through IVF. Samples are prepared using a modified next-generation sequencing method called FAST-SeqS and analyzed with a bioinformatics pipeline validated for detection of whole chromosome copy number, segmental aneuploidy (≥10 Mb), polyploidy and UPiD (for chromosomes 1–16, 18, and X). The ordering physician will receive a report with the test results, typically within 5–7 days from sample receipt.

RESULTS: Embryos will be diagnosed as “Normal” or “Abnormal.”

- **Normal** is defined as a test result that indicates that the sample submitted from the embryo has the correct number of chromosomes and therefore may be considered for transfer to the uterus.
- **Abnormal** is defined by a test result that indicates that the sample submitted from the embryo has the wrong number of chromosomes (**aneuploid**) and therefore may be considered unsuitable for transfer.

If the sample received is unacceptable for analysis or results cannot be obtained from the sample provided, it will be reported as **No Results**. Reasons for a no result embryo include insufficient amount of DNA present, poor DNA quality (often found in damaged or dying cells), or assay failure. On rare occasions results that did not meet the proper quality thresholds are reported out as **Indeterminate or Special Considerations** as an accurate result cannot be provided. For these situations, a re-biopsy is recommended if testing is still desired.

The results returned to your doctor come from the sample submitted. Your physician may use this information to help decide which embryo(s) to transfer. In rare cases, the sample submitted may not represent all of the cells in the rest of the embryo (mosaicism).

BENEFITS: PGT may increase the likelihood of a pregnancy and decrease the chance of miscarriage or failed implantation. Information obtained from PGT could also be beneficial to guide future attempts at pregnancy.

RISKS AND LIMITATIONS: It is important to note that PGT does not guarantee that a pregnancy will be achieved or that a pregnancy/child will not have a chromosome abnormality. PGT also does not guarantee the birth of a healthy baby or specific sex. The risks and limitations of embryo biopsy and PGT include but are not limited to the following:

- Current data suggests that children born after procedures requiring embryo biopsy, such as PGT, have a similar rate of birth defects to that of the general population conceived through IVF. However, embryo biopsy is still a relatively new technique and the potential for unknown consequences to a child cannot be excluded. PGT is recommended because your doctor believes that the benefits of PGT likely outweigh any risks associated with embryo biopsy.
- Invitae PGT identifies biopsy samples with extra or missing chromosomes or gross chromosomal material. Invitae PGT **does not** detect the following: balanced structural abnormalities including but not limited to balanced translocations and inversions; partial aneuploidy (including deletions, duplications, and unbalanced translocations) below the resolution of this assay; conditions caused by single gene mutations, such as sickle cell disease, cystic fibrosis or Tay-Sachs disease; uniparental disomy (UPD; two copies of a given chromosome, or chromosome region, from one parent and none from the other which can be associated with genetic syndromes and/or medical, cognitive, or physical disabilities) for chromosomes 17 and 19–22; all forms of polyploidy (a change in the number of whole sets of chromosomes), except haploidy/complete UPiD, triploidy, and some forms of tetraploidy (which are detectable); all instances of mosaicism (when cells within the same biopsy sample have a mixed chromosome makeup or are different between the biopsy sample and the embryo). Additionally, there is a 3–5% general population risk of birth defects. These may be due to genetic and/or non-genetic causes not detectable by PGT. As a result of these limitations, this testing may not be appropriate for some couples with a known balanced chromosome rearrangement or a significantly increased risk for chromosome rearrangement based on medical history. For this reason, consultation with a genetic counselor is available prior to testing. In addition, any known genetic conditions in the family should be discussed with your fertility doctor or a genetic counselor prior to initiating testing.
- Invitae PGT is not 100% accurate and there is a chance of a false negative or a false positive result. A false negative result will indicate an embryo has a normal number of chromosomes when there is actually a chromosome abnormality. A false positive result will indicate an embryo has an abnormal chromosome copy number when it is actually normal. Accurate results may not be obtained for reasons including but not limited to sample mix-up, technical problems or conditions beyond the detection limit of the technology employed, results with low resolution for partial aneuploidy assessment, sample contamination, the use of non-validated sample collection and handling procedures, and mosaicism (the biopsy sample is not representative of the embryo).

It is possible that none of the embryos tested will be chromosomally normal, or provide definitive results and thus no embryos may be appropriate for transfer. Sometimes for technical reasons, results cannot be generated. Additional samples (biopsies) may be needed, which may result in additional cost.

ADDITIONAL TESTING: PGT cannot guarantee the birth of a chromosomally normal child or a specific sex. Because of the limitations discussed above, prenatal diagnosis, either by chorionic villus sampling (CVS) at 10–12 weeks or amniocentesis at 15–18 weeks should be considered in order to verify the chromosome status of the fetus. PGT is not a replacement for prenatal screening/testing and you should undergo physician recommended prenatal testing based on your age and medical history even if PGT testing of your embryo(s) has been performed. CVS and amniocentesis have higher accuracy than PGT and can evaluate mosaicism and structural chromosome abnormalities. If a pregnancy loss occurs, chromosome studies on the products of conception may provide information relevant to future pregnancies.

ALTERNATIVES: The risks, benefits and alternatives of PGT testing can be discussed thoroughly with a genetic counselor, your doctor, or someone on their behalf. PGT is an optional test that is offered to increase the chance of having a successful pregnancy. You are not obliged to undergo PGT even if your physician recommends it. Proceeding with an IVF cycle without PGT is an alternative option. Prenatal screening, prenatal diagnosis, and ultrasound examination are available to evaluate chromosome abnormalities and/or birth defects once pregnant.

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CONFIDENTIALITY AND PRIVACY: I understand that my data and personal information will be stored and protected in compliance with applicable regulatory requirements (e.g., HIPAA and equivalent protections) and that Invitae keeps test results confidential and is in compliance with all HIPAA regulations. Invitae will release my PGT test results only to my certified health care professional(s) listed on the test requisition form unless otherwise directed by me (or a person legally authorized to act on my behalf) in writing. It has been explained to me that my clinical report is available to me upon request after it has been released to my healthcare professional(s) or upon request in accordance with applicable law. The Department of Health of my state and the Food and Drug Administration (FDA) may also inspect the records. The results provided are the number of chromosomes associated with each embryo sample submitted. Invitae does not assess the genome sequence or any changes in the genome sequence that may cause a genetic disease. We do not collect and are therefore unable to release to you any information about the genome of the embryo. I acknowledge that I have read and understand Invitae's Privacy Policy and Notice of Privacy Practices.

COSTS: Fees for PGT, including shipping of the biopsy sample, are in addition to any other costs associated with the IVF cycle (medications, egg retrieval, cryopreservation fees, biopsy fees, etc.). Fees must be either paid to Invitae directly or in some cases paid to your IVF center (depending on the payment protocol at your IVF center). All fees paid to Invitae are due prior to testing. If the PGT procedure is paid for but not performed, your payment will be fully refunded.

NEW YORK RESIDENTS: My sample can be retained for greater than 60 days after completion of the test in the event that additional genetic analysis is necessary: _____ INITIAL HERE INITIAL HERE

BY SIGNING BELOW, I ATTEST TO THE FOLLOWING:

1. I/we have read this Consent Form and have decided to proceed with PGT for chromosome aneuploidy assessment. I/we request that Invitae perform PGT on all embryo samples sent by my/our ordering physician. This consent is valid for a period of one (1) year from execution and applies to this and all future IVF cycles in which embryo testing with Invitae is requested during this one (1) year period, unless I/we specifically revoke this consent in writing and deliver the written revocation in a timely manner to Invitae.
2. I/we acknowledge that PGT can determine the number of chromosomes present in an embryo but that PGT cannot detect all chromosome abnormalities and does not guarantee a particular embryo sex and that my/our pregnancy must be followed by my/our IVF physician, obstetrician, and/or other appropriately trained healthcare professional. I/we understand that PGT is not a substitute for prenatal diagnosis (CVS or amniocentesis) and that other prenatal screening may be recommended regardless of the use of PGT. I/We understand that if I/we have questions about prenatal testing I/we may ask a genetic counselor or obstetrician.
3. If I/we have checked the "Yes" box below, I/we acknowledge that Invitae is committed to monitoring the outcome of PGT and understand that Invitae may contact me/us to inquire about the outcome of my/our IVF cycle. If I/we have checked the "Yes" box below, I/we acknowledge that I/we may be contacted throughout the course of the pregnancy and afterwards about the outcome and to follow the child. Any information received during these follow-up encounters shall remain strictly confidential. Information received will not be used for any purpose other than to advance the science of genetic testing of preimplantation embryos and will be de-identified (anonymous) for any public use. I/we understand that we can indicate "No" to opt out of re-contact for follow up purposes. Selecting "No" will not affect my/our ability to obtain the testing.
   a. PLEASE INDICATE SELECTION: Yes☐ No☐ INDICATE SELECTION
4. I/we have been given the opportunity to talk with a genetic counselor by telephone to ask questions about PGT and the information contained in this consent form. I/we understand that a genetic counselor is available to answer any additional questions. If I/we decide to complete this form prior to speaking with a genetic counselor, I/we acknowledge that I/we will be able to ask any questions that I/we may have with a genetic counselor during a future appointment.
5. I/we acknowledge that Invitae, its employees, directors and authorized agents may not be held liable in any manner whatsoever for any birth defects, chromosome abnormalities, false positive findings, false negative findings, shipping or transport errors or omissions, nor for any damage in contract or tort arising out of the PGT.

My signature below indicates I/we have read, or have had read to me/us, and understand the above information. The decision to consent to, or refuse, the above testing is entirely mine/ours. I/we have had the opportunity to discuss the pros and cons of proceeding, including the purposes, limitations, and possible risks, with my/our doctor, a genetic counselor, or someone my doctor has designated. I/we have all the information I/we want, and all my/our questions have been satisfactorily answered.

Patient signature	Patient name (please print)	Date
Partner signature	Partner name (please print)	Date

HEALTHCARE PROVIDER STATEMENT

By signing below, I attest that I am the referring physician or authorized healthcare professional. I have explained the purpose of test described above. The patient has had the opportunity to ask questions regarding this test and/or seek genetic counseling. The patient has voluntarily decided to have this test performed by Invitae.

Healthcare provider signature	Date