INVITAE

Informed Consent for Preimplantation Genetic Testing

FM160-3

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. 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.

   More information about PGT is available from my healthcare provider and can also be found on the Invitae website (www.invitae.com).

2. **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 my 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 my IVF clinic. Only the analysis of the biopsy samples occurs at Invitae. Results from the analyses of these samples are used to infer the chromosomal makeup of the rest of the embryo and resulting pregnancy/child.

   No testing apart from that which is ordered will be performed. Additional testing requires my additional, express consent.

   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.

3. **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.

4. **RESULTS:** 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 any information about the genome of the embryo.

   Embryos will be diagnosed as "Normal" or "Abnormal."

   a. **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.
   b. **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 my doctor come from the sample submitted. My 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).

5. **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.

6. **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:

a. 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 my doctor believes that the benefits of PGT likely outweigh any risks associated with embryo biopsy.

b. 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 my fertility doctor or a genetic counselor prior to initiating testing.

c. 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.

7. **ALTERNATIVES:** The risks, benefits and alternatives of PGT testing can be discussed thoroughly with a genetic counselor, my doctor, or someone on their behalf. PGT is an optional test that is offered to increase the chance of having a successful pregnancy. I am not obliged to undergo PGT even if my 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.

8. **DISCLOSURE OF TEST RESULTS:** Invitae's clinical reports are released only to the certified healthcare provider(s) listed on the test requisition form. Clinical reports are confidential and will only be released to other medical providers with my explicit written consent.

9. **NONDISCRIMINATION:** There are state and federal laws that prohibit discrimination against individuals for the purpose of employment or obtaining health insurance and that prohibit insurers and employers from seeking an individual's genetic information without consent. In accordance with such laws, Invitae will not disclose or interpret my genetic information for use by employers or insurers. However, it is my responsibility to consider the possible impact of my test results as they relate to insurance rates, obtaining disability or life insurance, and employment. The Genetic Information Nondiscrimination Act (GINA), a US Federal law, provides some protections against genetic discrimination. For more information on GINA, visit www.genome.gov/10002328.

10. **GENETIC COUNSELING:** I understand that Invitae recommends that I consult with a genetic counselor before consenting to this test and a genetic counselor or my healthcare provider about my results. For a list of medical geneticists and counselors who may be available in my area, I may visit the National Society of Genetic Counselors website at www.nsgc.org. Further testing or additional physician consults may be warranted.

11. **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 I acknowledge that I have read and understand Invitae's Privacy Policy and Notice of Privacy Practices (available at www.invitae.com/privacy).

I understand that I can opt-in so that Invitae may contact me to inquire about the outcome of my IVF cycle by contacting Invitae at privacy@invitae.com. If I opt-in, I acknowledge that I 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 understand that I can indicate "No" to opt out of re-contact for follow-up purposes.

12. **RESEARCH:** Sharing de-identified genetic data can significantly accelerate medical research for both individual patients and society as a whole. Invitae encourages patients to choose to share their genetic variants with the medical and scientific community to help accelerate our understanding of genetic conditions, improve genetic testing, find new therapies, and eventually prevent disease. Invitae will share results after they are de-identified, meaning that Invitae removes any information that identifies or could be used to identify me personally.

    a. **De-identified genetic information:** I understand Invitae may store and retain indefinitely at its discretion, except as prohibited by law, and use and/or disclose to third parties, including public databases, my de-identified genetic information for quality assurance, test development and/or validation, research, and/or educational purposes.

    b. **De-identified samples:** I understand Invitae may store and retain indefinitely at its discretion, except as prohibited by law, and use and/or share with third parties my de-identified samples for quality assurance, test development and/or validation, research, and/or educational purposes.

    c. **Future contact regarding research:** I permit Invitae to contact me in the future about research opportunities that may be related to my condition or my test results.

    All patients (other than residents of those states specifically identified below): I control how Invitae uses my data. I understand that I can contact Invitae at privacy@invitae.com if I would like to change my preferences with respect to how Invitae uses my deidentified data. If I choose to restrict the use of my de-identified genetic information or sample(s): (a) I understand that to the extent that such information has already been used or shared, it cannot be retracted or destroyed, and (b) I understand that my de-identified genetic information and/or sample(s) may still be used for quality assurance, test development and/or validation; shared with public databases; and/or (in connection with de-identified information) used or disclosed to third parties, not on an individual basis but as aggregated information for research or education purposes.

    Residents of New York or Alaska: I understand that my sample(s) (or my minor child's sample(s)) shall be destroyed no more than 60 days after they were taken or at the end of the testing process, whichever occurs later, unless a longer period of retention is expressly authorized. I understand that I can authorize a longer period of sample retention by contacting Invitae at privacy@invitae.com. I understand that if I authorize my samples to be retained longer, I can also allow the use of my de-identified samples for research and/or education by contacting Invitae at privacy@invitae.com. If I do not opt in, I understand that my de-identified samples will not be used for quality assurance, test development and/or validation; nor and/or used, disclosed to, or shared with third parties for research or education purposes. I further understand that I can allow the use of my de-identified genetic information for research and/or education, or to allow Invitae to contact me in the future regarding research opportunities by contacting Invitae at privacy@invitae.com. If I do not opt in, I understand that my de-identified genetic information may still be used for quality assurance, test development and/or validation; shared with public databases; and/or used, disclosed to, or shared with third parties, not on an individual basis but as aggregated information, for research or education purposes.

    Residents of Florida, Massachusetts, Minnesota, New Hampshire, Texas, Vermont and countries other than the United States: I understand that I can contact Invitae at privacy@invitae.com to opt-in to allow the use of my de-identified genetic information or samples for research and/or education, or to allow Invitae to contact me in the future regarding research opportunities. If I do not opt in, I understand that my de-identified genetic information and/or samples may still be used for quality assurance, test development and/or validation; shared with public databases; and/or used, disclosed to, or shared with third parties, not on an individual basis but as aggregated information, for research or education purposes.

13. **COSTS:** Fees for PGT 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 my IVF center (depending on the payment protocol at my IVF center). All fees paid to Invitae are due prior to testing. If the PGT procedure is paid for but not performed, my payment will be fully refunded.

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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. 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.
4. 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 THAT:

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

Patient signature	Date

Patient name (please print)	Email address

HEALTHCARE PROVIDER STATEMENT

By signing below, I attest that:

1. I am the referring physician or authorized healthcare provider;
2. I have explained the purpose of test described above;
3. The patient has had the opportunity to ask questions regarding this test and/or seek genetic counseling; and
4. The patient has voluntarily decided to have this test performed by Invitae.

Healthcare provider signature	Date