



PATIENT CONSENT FORM
Preimplantation Genetic Screening (PGS)
24 Chromosome Aneuploidy and Translocation Screening with aCGH

PREIMPLANTATION GENETIC SCREENING FOR ANEUPLOIDY SCREENING

INTRODUCTION

Preimplantation genetic screening (PGS) is used in conjunction with in-vitro fertilization (IVF) to screen embryos for numerical chromosomal abnormalities prior to transfer. The information obtained from PGS helps IVF physicians and patients decide which embryos to transfer.

Aneuploidy screening: Normally there are 23 pairs of chromosomes in each human cell, for a total of 46 chromosomes. Usually half of the chromosomes come from the mother (egg) and the other half from the father (sperm). PGS is used to identify embryos with extra or missing chromosomes. Such numerical abnormalities in chromosome amounts are called aneuploidy. Aneuploidy is responsible for the vast majority of spontaneous miscarriages, and the birth of a child with aneuploidy can result in birth defects and mental retardation. One of the most common examples of a viable aneuploidy is an extra copy of chromosome 21 (Down syndrome or trisomy 21). The chance of having aneuploid embryos increases with maternal age. Identifying chromosomally normal embryos prior to transfer increases the chances of achieving a successful pregnancy.

PROCEDURE

Genetic Counseling: It is recommended that you have a consultation with a genetic counselor that specializes in PGS before undergoing PGS. You have the option to make an appointment for a phone consultation prior to signing this consent form. The genetic counselor will describe the benefits and risks of PGS for aneuploidy as well as answer any additional questions you may have. This consultation can be arranged by calling the Blastogen reference laboratory directly at 310-618-0618, or can be arranged by your IVF clinic. Please note that Blastogen requires you to call at least 3 business days prior to your biopsy date to schedule the appointment. Blastogen genetic counselors are also available to review the results after the testing has been completed.

Biopsy (Embryo or 1st/2nd Polar Body), Cell Preparation and Transport: Biopsy, cell preparation and transport procedure will take place through your IVF clinic. Blastogen can analyze biopsies from Day 3 or Day 5 embryos or polar body biopsies from the egg. Your physician will recommend the type of biopsy procedure. For embryo biopsy, the embryologist at your center will remove a single cell for Day 3 biopsy or multiple cells for Day 5 biopsy. The embryos or eggs will remain at your IVF center. After the biopsy procedure, cell(s) are washed and transferred to a small test tube. Then the samples are transported by special courier for either same day delivery or overnight delivery (i.e. Marken, FedEx etc.) to the Blastogen Laboratory. Transportation of samples is not without risks. Samples may be damaged or destroyed despite special and careful packaging. Samples may also be delayed because of weather, air travel problems or other unforeseen technical reasons beyond the control of Blastogen. Rarely, samples do not arrive in the reference laboratory or are damaged during transport. There is also a chance that the sample received in the Blastogen laboratory is unacceptable for analysis and results cannot be obtained. Blastogen is not responsible for any sample until it arrives at the Blastogen laboratory.

Analysis and Reporting of Results: The analysis of the cells is performed by Blastogen. To analyze the genetic material (DNA) within the embryo cells, Blastogen uses an amplification technique called polymerase chain reaction (PCR). This amplification process produces enough DNA to use a second technique, known as array comparative genomic hybridization, (aCGH) with the 24Sure™ (BlueGnome™) array. Array-CGH assesses the amount of DNA derived from each chromosome,



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revealing whether or not there are a correct number of chromosomes. Your IVF physician will receive a report with the test results about 12 hours after the receipt of your samples at the BlastoGen laboratory. Your physician will decide which embryos to transfer based, in part, on these results.

CONFIDENTIALITY AND DISPOSAL OF SAMPLES:

BlastoGen keeps test results confidential and is in compliance with all Health Insurance Portability and Accountability Act (HIPAA) regulations. BlastoGen will release your test results only to your designated IVF physician unless otherwise directed by you (or a person legally authorized to act on your behalf) in writing, or as otherwise required by federal and California state laws. The Department of Health of your state and the Food and Drug Administration (FDA) may also inspect the records.

Biopsied cells will not be used for any purpose other than PGS. All samples are discarded within 60 days after results are reported or the test is discontinued for any reason.

COSTS:

Fees for PGS are in addition to any other costs associated with the IVF cycle. Fees must be either paid to BlastoGen directly or paid to your IVF center (depending on the payment protocol at your IVF center). All fees paid to BlastoGen are due prior to embryo biopsy. Your IVF center finance department or a BlastoGen financial coordinator will advise you of the fees. If the PGS procedure is paid for but not performed (for any reason including cancellation, lack of suitable embryos for biopsy, or transportation delay), your payment will be refunded.

RISKS AND LIMITATIONS

PGS carries a set of limitations and risks, outlined below.

1. Risks of embryo biopsy/polar body biopsy:

Thus far, babies born after PGS or other types of procedures that include embryo biopsy have had a similar rate of birth defects to babies in the general population. The removal of the polar bodies does not adversely affect the subsequent development of the embryo. For embryo biopsy, there may be a risk of decreased viability of the embryo due to the biopsy procedure itself. Although data has shown that embryo biopsy has no adverse impact on growth or medical outcomes, the technique is still relatively new and the potential for unknown consequences to a live born baby cannot be excluded. However, your IVF physician has recommended PGS because the doctor believes that the benefits of PGS are likely to outweigh the risks associated with embryo biopsy.

2. PGS cannot detect mosaicism:

PGS cannot detect mosaicism, in which there is more than one chromosomally distinct cell in the same embryo. If mosaicism is present, the biopsied cell(s) may not be representative of the entire embryo and PGS results will not be accurate. See "Misdiagnosis by Chromosomal Mosaicism" below.

3. PGS cannot detect single gene mutations:

PGS for aneuploidy does not analyze specific genes and cannot detect conditions caused by single gene mutations, such as Sickle Cell anemia, cystic fibrosis or Tay-Sachs disease. Any known genetic conditions in the family should be discussed with your fertility doctor.



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4. PGS cannot detect uniparental disomy (UPD):

UPD is the presence of two copies of a given chromosome from one parent and none from the other. UPD for certain chromosomes is associated with particular genetic syndromes or medical, cognitive or physical disabilities. BlastoGen is unable to detect UPD via PGS.

5. PGS cannot detect very small imbalances:

PGS technology is designed to test for aneuploidy (whole chromosomes that are extra or missing). It can also detect partial aneuploidy, including deletions, duplications, and unbalanced translocations, depending on the size of the chromosome segment involved. Extra or missing chromosome segments, smaller than 6 MB, usually cannot be detected.

6. PGS cannot detect balanced structural abnormalities:

PGS cannot detect structural abnormalities unless there is an imbalance in genetic material. There are multiple chromosomal abnormalities, including but not limited to balanced translocations and inversions that BlastoGen cannot test for.

7. PGS cannot detect polyploidy:

PGS cannot detect polyploidy, in which there is a numerical change in a whole set of chromosomes. Polyploidy may arise from fertilization of an egg by more than one sperm (polyspermia), fertilization of a diploid egg, or fertilization by a diploid sperm.

8. PGS cannot detect all birth defects:

PGS cannot detect all potential birth defects and can only detect birth defects caused by aneuploidy and imbalances greater than 6MB. **There is a 3-5% risk in the general population of birth defects. These may be caused by genetic and/or non-genetic etiologies.**

9. Misdiagnosis:

With each embryo sample analyzed, there is a chance for misdiagnosis. Misdiagnosis can be due to test error or due to mosaicism even when there is no testing error on the particular sample analyzed.

Misdiagnosis due to Test Error: PGS testing cannot be precise and will not be exact.

There remains an empirically determined 1-2% chance of a misdiagnosis, either by a false negative or a false positive result. A false negative result will indicate an embryo has a normal number of chromosomes when, in reality, it contains a chromosomal abnormality. A false positive result will indicate an embryo is aneuploid when it is actually chromosomally normal.

Misdiagnosis due to Chromosome Mosaicism: Mosaicism occurs by chance during embryonic development and can cause a PGS misdiagnosis if the cell(s) that is (are) biopsied and tested is (are) not representative of the embryo. By definition, PGS cannot detect mosaicism when only one cell or a few cells are biopsied and analyzed. To conclusively determine whether an embryo is mosaic, *all* cells of the embryo must be analyzed, which would result in destruction of the embryo.

10. No diagnosis:

There is a chance of unpredictable and uncontrollable problems with transportation, such as weather and air travel issues, or other circumstances beyond the control of BlastoGen that would not allow results to be obtained in time for embryo transfer. There is also a chance that the sample received in



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the Blastogen laboratory is unacceptable for analysis and results cannot be obtained from the sample provided.

On rare occasions genetic testing cannot be performed on biopsied eggs or embryos due to improper biopsy techniques such as a) removing an anucleated cell; b) cell lysis during the biopsy procedure; c) cell loss during washing and transfer; and, d) unexpected technical problems during the procedure.

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 may be aneuploid. Transferring embryos without a diagnosis or with an abnormal diagnosis may lead to an abnormal pregnancy.

11. Inconclusive results:

A statistical model is used to determine the number of chromosomes for each embryo sample. In some cases, due to degraded DNA, or unusual biological processes, or other unusual effects in a sample, the data will not conform to the statistical model. In these cases, the results will be reported as inconclusive.

12. No normal embryos:

There is a chance that all embryo samples tested during an IVF cycle will be found to have aneuploidy and no embryos will be suitable for transfer. Likewise, there is also a chance that an embryo sample will be found to be chromosomally normal but the embryo may not develop normally and will not be selected for transfer.

13. Intracytoplasmic Sperm Injection (ICSI):

ICSI as a method of fertilization is recommended, but not required prior to PGS. If ICSI is not performed, there is an increased risk of “no results” on one or more samples due to contamination of the sperm. Please consult with your IVF physician and discuss the risks and benefits of different fertilization approaches.

BENEFITS

PGS may help couples at higher risk for aneuploidy achieve ongoing pregnancies. Possible risk factors for aneuploidy include women aged 35 and older, multiple early miscarriages, prior failed IVF cycles, previous pregnancies with chromosomal abnormalities, and unexplained male-factor infertility.

In the majority of cases, aneuploid embryos are indistinguishable morphologically and developmentally from chromosomally normal ones. Thus, without genetic testing, an embryologist cannot differentiate normal embryos from aneuploid embryos.

Some studies have shown that PGS may increase the chance for a successful pregnancy and live birth in women at increased risk for aneuploidy, while others studies have not. PGS is a new and evolving technology. To date there have not been any prospective randomized research studies have been done to date on the use of PGS in IVF cycles correlated to pregnancy outcomes. As further data is collected, the PGS technology and the reporting of the results from the tests are likely to undergo further refinement.

ALTERNATIVES



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The risks, benefits and alternatives of PGS testing should be discussed thoroughly with your genetic counselor, obstetrician or the person performing/ordering the tests. PGS for aneuploidy is an optional test that is offered to increase the chance of having a healthy live born baby. You are not obliged to undergo PGS even if your physician recommends it. Proceeding with an IVF cycle without PGS is an alternative option. Prenatal screening, prenatal diagnosis, and ultrasound examination are available to evaluate chromosomal abnormalities and/or birth defects.

RECOMMENDED FOLLOW-UP TESTING

PGS cannot guarantee the birth of a chromosomally normal child. Because of the chance of misdiagnosis, the inability to detect mosaicism and structural abnormalities, and the investigational nature of PGS, ongoing pregnancies resulting from PGS for aneuploidy during IVF, **should always** be followed by prenatal diagnosis, either by chorionic villus sampling (CVS) at 10-12 weeks or amniocentesis at 15-18 weeks to confirm a chromosomally normal fetus. PGS should not be considered a replacement for prenatal testing. CVS and amniocentesis have higher accuracy than PGS and can evaluate mosaicism and structural abnormalities. Your obstetrician can perform these tests. If a pregnancy loss occurs, we recommend that chromosome studies be performed on the products of conception.



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CONSENT FOR PGS

I/we have read this Patient Consent Form completely and have decided to proceed with PGS for aneuploidy. I/we request that BlastoGen perform PGS on all embryo samples sent by our IVF doctor during our IVF cycle. This consent applies to this and all future IVF cycles in which I request embryo testing with BlastoGen.

I/we acknowledge that PGS has both benefits and risks, some of which may as yet be unknown. I/we also acknowledge that PGS is a new technology which may encounter data not yet seen, logistical challenges not yet encountered, or other unforeseen issues that may affect the quality of the results, and accordingly both the test and reporting of results is likely to undergo further refinement in the future.

I/we acknowledge that PGS can determine whether the embryo could be affected by a chromosomal abnormality. However, we understand that PGS cannot detect all chromosome abnormalities and that our pregnancy must be followed by our IVF physician, obstetrician, and/or other appropriately trained healthcare professional. **BlastoGen strongly encourages prenatal diagnosis (CVS or amniocentesis) during the resulting pregnancy in order to confirm the results of PGS. We understand the need for standard prenatal testing *remains the same* whether or not PGS for aneuploidy is performed. We understand that if we have questions about prenatal testing we may ask our obstetrician or request a referral to a genetic counselor.**

I/we acknowledge that BlastoGen is committed to monitoring the outcome of PGS and understand that BlastoGen may contact me for information regarding the outcome of my IVF cycle. 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. Your information 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 have been given the opportunity to talk with a BlastoGen genetic counselor by telephone and to ask questions about PGS and the information contained in this consent form. I/we acknowledge that if I/we have additional questions, I/we can arrange to speak with the BlastoGen genetic counselor again. If I/we decide to complete this form prior to speaking with the genetic counselor, I/we acknowledge that I/we will be able to ask any questions that I/we may have with the genetic counselor during a future appointment. I/we acknowledge that my/our request for genetic counseling must occur at least three business days before my biopsy date which means that if I/we am deciding to do testing within three days of my biopsy date. I/we agree to have testing performed without first speaking to the BlastoGen genetic counselor and agree to pay all associated testing fees.

I/we acknowledge that BlastoGen may not be held liable in any manner whatsoever for any birth defects, chromosomal abnormalities, false positive findings, false negative findings, shipping or



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transport errors or omissions, nor for any damage in contract or tort arising out of Blastogen PGS screening.

I/we acknowledge that any legal controversy, dispute or disagreement arising out of the services provided by Blastogen or any subsidiary thereof shall be settled by binding arbitration by the American Arbitration Association, under the applicable Arbitration Rules then in effect. Any award of the arbitrator(s) may be entered as a judgment in any court of competent jurisdiction. Information may be obtained and claims may be filed in any California office of the American Arbitration Association. Any such arbitration shall take place at the American Arbitration Association office San Francisco, California; or if no such office exists, at the American Arbitration Office closest to Blastogen’s corporate headquarters at the time of the filing of the arbitration. All disputes shall be decided under the laws of the State of California.

By initialing below and signing this Patient Consent Form you are: (i) agreeing to the arbitration agreement set forth above, and are giving up your right to a jury trial as to all claims covered by such arbitration agreement; (ii) waiving the right to have evidence admitted only if it is deemed admissible under the applicable rules of evidence; (iii) waiving the right to certain discovery procedures available under the California Code of Civil Procedure; and (iv) acknowledging that you have been advised to and have had the opportunity to consult with independent counsel concerning this arbitration agreement.

(Patient Initials Here)

My/our signature below means that I/we have read and understand this Blastogen Patient Consent Form. I/we have been encouraged to ask questions about any portion of this Blastogen Patient Consent Form and to consult with family, friends and/or medical or legal advisors as I/we see fit. This Patient Consent Form is the only agreement between Blastogen and me to provide PGS for aneuploidy. I/we explicitly acknowledge that this Patient Consent Form obligates me to participate in Arbitration should any dispute arise out of this agreement. I/we consent to PGS for aneuploidy by Blastogen using aCGH technology.

Signature of Patient

Signature of Spouse/Partner

Date

PRINTED NAME

PRINTED NAME



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PGS FOR UNBALANCED CHROMOSOMAL REARRANGEMENT SCREENING
ADDENDUM

Unbalanced rearrangement screening is offered to patients who have been pre-identified as being a carrier of a balanced translocation or inversion. The above information regarding PGS for aneuploidy also applies to unbalanced rearrangement screening with the following additions or modifications:

INTRODUCTION

Two types of chromosomal rearrangements are translocations and inversions. An individual with an inversion has a piece of a chromosome that has been flipped within the chromosome. A translocation is when there has been an exchange of genetic material between non-homologous chromosomes. Chromosomal rearrangements are considered “balanced” when there is a normal amount of genetic material and “unbalanced” when there is extra or missing chromosomal material. Someone with a balanced rearrangement (a carrier) usually has no health or developmental problems, although they may sometimes have difficulties conceiving. The offspring of a carrier of balanced rearrangement can inherit an unbalanced rearrangement, which may lead to failed implantation of an embryo, a miscarriage during pregnancy, or a child being born with mental and physical problems. An offspring that inherits the balanced rearrangement should not have any health problems caused by the rearrangement. Rarely, a rearrangement, thought to be balanced, in fact includes an unbalanced element too tiny to be detected by standard cytogenetic chromosome analysis that may lead to physical or cognitive problems.

PROCEDURE

Biopsy: Polar body biopsy of the egg would not be appropriate for unbalanced rearrangement screening if it is the father who carries the balanced rearrangement.

Analysis: The unbalanced rearrangement would be identified as gains and/or losses of segments at the ends of the chromosomes. Unbalanced rearrangement screening uses an optimized array platform with higher probe density at chromosome ends.

Additional Requirements: Prior to starting a new IVF cycle, karyotyping of the balanced translocation or inversion carrier must be performed at a CLIA certified cytogenetic laboratory, and the result report must be submitted to Blastogen for review.

CONFIDENTIALITY AND DISPOSAL OF SAMPLES

See PGS for aneuploidy section above.

COSTS

See PGS for aneuploidy section above.

RISKS AND LIMITATIONS

The risks of unbalanced rearrangement screening are the same as above. Two limitations of both PGS for aneuploidy and PGS for unbalanced rearrangement screening are emphasized below. All other limitations of PGS for aneuploidy also apply to unbalanced rearrangement screening.



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1. PGS cannot detect very small imbalances:

PGS technology is designed to test for aneuploidy (whole chromosomes that are extra or missing). It can also detect partial aneuploidy, including deletions, duplications, and unbalanced rearrangements inherited from a parent with a translocation or inversion, depending on the size of the chromosome segment involved. Unbalanced rearrangements that have extra or missing chromosome segments smaller than 6 MB usually cannot be detected.

2. PGS cannot detect balanced structural abnormalities:

PGS cannot detect structural abnormalities unless there is an imbalance in genetic material. There are multiple chromosomal abnormalities, including but not limited to balanced translocations and inversions that that BlastoGen cannot test for. Array CGH cannot distinguish an embryo that did not inherit a rearrangement from an embryo that inherited the balanced rearrangement.

BENEFITS

Identifying embryos that have inherited an unbalanced rearrangement can help patients and doctors make informed decisions about which embryos to transfer. Unbalanced rearrangement screening is appropriate for individuals who are carriers of a previously identified balanced translocation or inversion. Risk factors for being a carrier of a balanced translocation or inversion include unexplained male-factor infertility, multiple miscarriages, and a family history of birth defects.

ALTERNATIVES

See PGS for aneuploidy section above. Inversions and translocations, both balanced and unbalanced, can be detected prenatally through either CVS or amniocentesis. Prenatal screening on maternal serum cannot detect unbalanced rearrangements.

RECOMMENDED FOLLOW-UP TESTING

See PGS for aneuploidy section above. **BlastoGen recommends confirmatory prenatal diagnosis by CVS or amniocentesis.**

My/our signature below means that I/we have read and understand this PGS for Unbalanced Chromosomal Rearrangement Screening Addendum to the BlastoGen Patient Consent Form. I/we consent to PGS for unbalanced rearrangement screening by BlastoGen using aCGH technology.

Signature of Patient

Signature of Spouse/Partner

Date

PRINTED NAME

PRINTED NAME