Consent to treatment involving pre-implantation genetic testing for aneuploides (PGT-A)

About the patient (Please check your details carefully)

First name

Surname

Date of birth

Patient I.D.

Information for patients wanting to consider PGT-A with NGS testing

What are chromosomes?

Chromosomes are small rod shaped structures that exist in virtually every cell of the body. Each cell should have exactly 46 chromosomes (23 pairs). In each pair one chromosome is inherited from the mother and one from the father. The chromosomes carry the genes; the chemical instructions that tell the embryo how to develop into a baby. In some ways, the genes can be thought of as blueprints, describing how to build a body out of all the different types of tissues.

Why look at chromosomes in eggs and embryoss?

Research has shown that chromosome abnormalities are very common in eggs and embryos. Chromosomal abnormalities/aneuploidies are responsible for the vast majority of spontaneous miscarriages and can result in birth defects. The chance of having aneuploidy embryos increases with maternal age and with sperm with abnormal parameters. For women in their early thirties about one quarter of the eggs and embryos have an abnormal number of chromosomes, but for women over 40 it is usual for more than half of the embryos produced to be abnormal.

What happens if an embryo has an incorrect number of chromosomes?

If a chromosome is lost, if one of them is duplicated, or if the chromosome has a small loss or gain of a chromosome the genetic instructions no longer make sense and the embryo will be unable to form a healthy baby. It would be like trying to build a complex machine with a page from the blueprints missing. With very few exceptions, an embryo with the wrong number of chromosomes will not produce a baby. Most abnormal embryos either fail to implant in the womb or miscarry during pregnancy.

Might it be a good idea to test IVF embryos for chromosome abnormalities?

In theory, embryos with a correct number of chromosomes should have a better chance of producing a baby than embryos with an abnormal set of chromosomes. If they could be identified during the IVF procedure, and given priority for transfer to the womb, pregnancy rates are predicted to be increased. It is also likely that the risk of miscarriage and genetic conditions such as Down syndrome would be reduced, since these problems are usually associated with chromosomally abnormal embryos. However the transfer of normal embryos does not guarantee a pregnancy and a live birth.

Are chromosomes routinely tested during IVF procedures?

In most cases the answer to this question is no. The examinations routinely undertaken in the IVF laboratory, in order to determine which embryo is the most likely to produce a baby, do not reveal which embryos have the correct number of chromosomes. Chromosome abnormalities are invisible to traditional (morphological) embryo assessment.

How can we test embryos produced using IVF to see if they have the correct number of chromosomes?

Several different methods have been utilised over the years for counting the number of chromosomes in embryos. This was always known as preimplantation genetic screening (PGS) historically. The testing is now termed preimplantation genetic testing for aneuploidies (PGT-A). PGT-A involves the removal of 5-10 cells from embryos that have reached the blastocyst stage on day 5 or day 6. The embryos are then frozen. The cells are then sent for analysis using next generation sequencing (NGS) testing of the cells to find out the number of chromosomes. It takes approximately 2 weeks to get the results. If the cells are found to have an abnormal chromosome number (aneuploid) then the remainder of the embryo is also predicted to be aneuploid and therefore are predicted to be associated with higher rates of miscarriage and a failure to implant. If the test shows that the blastocyst has the correct number of chromosomes (euploid) then the blastocyst can be thawed out and replaced in an FET cycle.

What is the accuracy of NGS?

The accuracy of NGS for detecting chromosomal abnormalities is predicted to be about 98%.

What are the risks and limitations of PGT-A?

There is a very small risk that a blastocyst may not survive the removal of cells (biopsy). There is a small risk that the embryo will not survive the cryopreservation procedure. If an embryo is damaged by biopsy or cryopreservation it will be unable to produce a baby. The risk to the blastocyst of damage during biopsy or cryopreservation is thought to be less than 5%.

Not all chromosome abnormalities can be detected with NGS. These include but are not limited to complex chromosomal abnormalities, some translocations and inversions, polyploidy (where a whole extra set of chromosomes are present in the embryo), Uniparental Disomy, or trisomy caused by Robertsonian translocations. Certain birth defects caused by genetic and/or non-genetic etiologies will not be detected by PGT-A.

Can I have a fresh transfer after PGT-A?

It is not possible to have a fresh transfer of PGT-A tested blastocysts, as the wait time is 2 weeks for NGS results.

Does PGT-A replace the need for routine prenatal testing?

Although PGT-A is likely to reduce the risk of having a pregnancy affected by a chromosome abnormality, it is not 100% accurate and therefore cannot guarantee it. Misdiagnosis can be positive, or negative. For this reason, we strongly recommend that you have a prenatal test (for example harmony screening) and if necessary more invasive testing if it is recommended to you by your doctor. This will provide a more definitive diagnosis and may detect some subtle abnormalities that PGT-A cannot. A miscarriage may still occur, even after the transfer of normal blastocysts.

What sort of results can I expect following PGT-A testing of my embryos, and what are the 'rules'?

We will get a report with a result for each of the blastocysts that are tested. In most cases, some of the blastocysts will be found to have the correct number of chromosomes, and will therefore be called normal, or EUPLOID, and some will be found to be abnormal or ANEUPLOID. However, it is possible that the test may reveal that none of the blastocysts are normal, in which case there will be no embryos available for transfer. The likelihood that this will happen is dependent on your age and the number of eggs and blastocysts produced. Additionally, about 5% of the blastocysts tested do not give a result. Blastocysts without a result can still be transferred, but it will not be possible to say whether or not they have the correct number of chromosomes. The potential advantages of PGT-A will therefore not apply to such blastocysts.

The misdiagnosis rate with NGS on blastocyst stage embryos is low, at 1-2%. This is when the cells biopsied do not accurately represent the rest of the embryo. For example, the results may come back as abnormal when in fact the blastocyst is normal or vice versa. There is also a possibility that the blastocysts may be mosaic. This is when the cells biopsied contain both normal and abnormal cells at varying percentages. The risk of embryo mosaicism being detected when biopsied at the blastocyst stage is thought to be about 2%. Depending on the percentage of mosaicism present we will advise accordingly the best course of action for that particular embryo based on genetic advice from the external genetic laboratory. We will also organise follow up genetic counselling for these embryos if it is recommended.

Can we use NGS to test for translocations or single gene disorders?

We can now use NGS to test blastocysts for most known translocations. It is not possible to use NGS for single gene disorders. If you have, or think you may have, a translocation or a single gene disorder in your family, please contact a member of the embryology team before you commence treatment as you may need more comprehensive testing.

Is there anything that isn't allowed under HFEA regulation?

We are not allowed to carry out sex selection for social reasons. Sex selection can only be carried out when there is a known risk of serious physical or mental illness or disability to a particular gender. In this case, the unaffected gender will always be selected over an embryo of the affected gender. The HFEA will also not allow embryos that have been biopsied to be transferred with embryos that have not been biopsied.

The costs of PGT-A with NGS

- Costs per embryo tested are as specified in the Lister Fertility Clinic's current price list.
- Blastocyst fee as specified in the Lister Fertility Clinic's current price list.
- Cryopreservation, if you have a fresh transfer and biopsy of any excess blastocysts - as specified in the Lister Fertility Clinic's current price list. This fee is included in your cycle cost if you do not have a fresh transfer
- Normal IVF fees will also be charged

Is there anything else I need to be aware of?

For PGT-A to be able to take place the egg collection for the IVF cycle **must happen** on a **Wednesday, Thursday, Friday or Saturday**. This is to ensure that the biopsy of the embryos happens on a weekday. As such, plans need to be put in place and therefore PGT-A must be requested before starting an IVF cycle.

Alternatives to NGS

Alternatives to NGS include standard prenatal testing for abnormalities (harmony testing, chorionic villous sampling, amniocentesis, ultrasound examination). These tests do not help to identify the embryo most likely to produce a baby, but can be used after a pregnancy has begun to identify problems with the foetus. You do not have to undergo NGS even if your doctor recommends it. Before you decide to have NGS, it is strongly recommended that you attend a genetics open evening. This can be booked in with the embryology team. If you wish to be referred to a genetic counsellor, please let us know. NGS should not be considered substitutes for routine prenatal testing.

Retention of samples

The cells to be tested are destroyed during the process of the analysis and cannot be returned to the embryo or used for any other purpose except the NGS test. DNA from these cells will be stored for a minimum of thirty years. We send sample to Igenomix. By agreeing to the NGS process, you must give your consent to us to share medical information with Igenomix.

HFEA opinion

The HFEA stated "that three small studies have now shown that PGS carried out at a later stage, the blastocyst embryo on day 5 or 6, might be helpful in selecting a viable embryo to transfer in younger patients who are typically under 37 with no history of miscarriage or failed IVF cycles. However, more evidence is needed to confirm these findings."

However, the HFEA, to the surprise of many clinicians and embryologists recently changed the traffic light grading from amber to red, suggesting no evidence of benefit, but there will be a considerable clinical consensus attempting to reverse this.

We strongly believe that the evidence shows that when used correctly in a particular patient group, PGT can be of a significant benefit by reducing the amount of cycles needed to achieve a successful ongoing pregnancy. By reducing the time it takes to achieve this 'end result' the impact of treatment both emotionally and physically is alleviated considerably.

You can read more about the HFEA traffic light system on fertility "add ons" in the information provided in your cycle packs or on the following link **https://www.hfea.gov.uk/treatments/explore-all-treatments/treatment-add-ons/**.

A fertility "add-on" is an "optional extras that you may be offered on top of your normal fertility treatment, often at an additional cost. They're typically emerging techniques that may have shown some promising results in initial studies but haven't necessarily been proven to improve pregnancy or birth rates."

Please contact the Lab on 020 7881 4041 or lab1@lfclinic.com to arrange this and/or if you have any further questions regarding PGT-A.

1 All Patients

☐ I/We confirm the following: *

- I/We have had the opportunity to discuss this procedure with the clinical staff of the Lister Fertility Clinic
- I/we understand the purpose of the test and what the procedure involves and am/are aware of the risks and limitations of both the embryo/blastocyst biopsy and diagnostic procedures. I/we understand that transfer may occur on a frozen cycle. I/we understand the extra costs for this procedure.
- There is no guarantee that embryos/blastocysts will survive the biopsy or thawing process, and hence there may be no blastocysts available for transfer. Abnormal embryos/blastocysts will be perished under laboratory conditions. Biopsied embryos cannot be transferred with non-biopsied embryos. I/we also understand that the transfer of any embryos/blastocysts will not guarantee a successful outcome.
- I/we understand that the DNA may fail to amplify and result in embryos with NO result. These embryos can be transferred but are to be treated as untested. I/we am/are also aware of the risk of misdiagnosis due to embryo mosaicism. For these reasons I/we have been advised to undergo a pre-natal diagnosis procedure following pregnancy.
- I/we understand that gender selection for social reasons is not permissible under current UK regulation.
- I/we have read the patient information on genetic testing and understand all aspects of testing. I/we are happy for the Lister to share medical information with Igenomix. I/We are happy for Igenomix to perform PGT-A on our samples.
- I/We understand that the sample(s) may be stored at Igenomix for future testing related to specific diagnosis for the patient.
- I/We understand that the Lister and Igenomix will not be responsible for any sample degradation that results in a no result embryo, either from transportation issues or sample preparation.
- I/We understand that after the genetic test has been completed a small amount of surplus DNA may be left over. I/we consent to the anonymous use of this material for follow-up testing, either using the original method or alternative methods, allowing confirmation of the diagnosis. I/we also consent for our clinical information/samples to be used for training and research, audit, and quality assurance purposes.
- I/We understand that the HFEA "traffic light rating" for PGT-A on Day 5, suggesting that there is a growing body of evidence which is showing promising results but where further research is still required.

2 Only Patients with X-Linked condition

ONLY COMPLETE THIS SECTION IF YOU HAVE A X-LINKED CONDITION

☐ I/We confirm the following:

- Gender selection in this situation is only allowed due to the presence of the X-Linked condition that we carry.
- The transfer of a EUPLOID (normal) FEMALE embryo does not guarantee a pregnancy and live birth outcome.
- I/We have seen a genetic counsellor and understand all options involved in pre-conception and pre-natal screening.
- I/We understand that there is a possibility that no normal or female embryos will be identified following PGT-A using NGS testing for sex selection. In this situation a normal male embryo may be transferred and pre-natal testing will be necessary.

3 All Patients

I/We confirm that I/we have discussed our clinical scenario with our clinician and (select one of the following options, it is important that you discuss and agree your selection with your partner): *

☐ I/We will **under no circumstances** transfer untested embryos, so will not commence progesterone following egg collection.

☐ I/We **may under certain circumstances** transfer untested embryos (for example, if not of an ideal quality for biopsy and freeze), so will start progesterone following egg collection to allow for this scenario.

I/We confirm that I/we clearly understand the following:

- Egg collection must happen on a Wed, Thurs, Fri or Saturday to allow for PGT- A to be possible
- The embryo must be a blastocyst and be of a suitable grade for biopsy and freezing,
- All embryos will be frozen post biopsy D5 and D6 whilst results are pending
- The price of testing will include freezing but not the subsequent FET
- Results will take approximately 2 weeks
- All embryos must be Assisted Hatched on day 3 of embryo development for PGT-A to be possible
- The transfer of a EUPLOID (normal) embryo does not guarantee a pregnancy and live birth outcome.
- There is a risk of Mosaicism and misdiagnosis. If necessary, a genetic counsellor will be made available to consult on the embryos with a mosaic result
- Pre-Natal testing is still recommended.
- There is a risk of no result due to the failure of the DNA to amplify.
- There is a risk of no embryos being available for transfer either pre-or post-testing
- I can confirm that I have read the patient information and watched the PGT video online, and understand the process and the limitations. The charges per embryo tested are as specified in the Lister Fertility Clinic's current price list. Charges apply regardless of result (i.e. Normal / Abnormal / No result / Mosaic / inconclusive)

Date