

Preimplantation Genetic Testing

Background

Preimplantation genetic testing is used in conjunction with in vitro fertilization (IVF) and allows identification of embryos that are; 1) free of chromosome abnormalities, or 2) free from known genetic disorders. These procedures are known as preimplantation genetic screening (PGS) and preimplantation genetic diagnosis (PGD) respectively. Transferring embryos with the correct number of chromosomes may increase the chance of a successful pregnancy. For couples who are at risk of passing on an inherited condition, only unaffected embryos are chosen for replacement. Therefore preimplantation genetic testing avoids the need to terminate a pregnancy as may occur when a defect is identified using prenatal testing such as amniocentesis or chorionic villous sampling.



How Does Preimplantation Genetic Testing work?

Preimplantation Genetic testing requires couples to go through routine IVF egg collection and Intracytoplasmic sperm injection (ICSI; refer to information sheets 12.3.8) so that their embryos can be tested before being transferred to the woman's uterus. Three days after fertilization when the embryos are at the 5 to 8 cell stage of development, one or two of the embryonic cells can be removed by embryo biopsy. The embryo biopsy procedure involves making a fine hole in the zona pellucida (outside shell surrounding the embryo) and gently removing the cell(s). The cells are then processed and tested to see if they have the normal number of chromosomes

(PGS), or are free from the genetic condition being tested for (PGD). The embryos that are identified as being normal can then be transferred to the woman's uterus in the hope of establishing a healthy pregnancy.

The embryo biopsy procedure is routinely performed in many centers around the world and does not appear to harm the developing embryo. It has been estimated that biopsy is successful in well over 98% of embryos.

PGS

Testing of the biopsy cells to detect the number of chromosomes is done using a technique called array comparative genomic hybridization (aCGH) which

makes thousands of independent measurements of all the chromosomes at the molecular level using a test called 24sure.

Who might benefit from PGS?

The *WA Human Reproductive Technology Act 1991* allows PGS to be done in the following situations:

- Female is 35 or over
- 3 or more IVF cycles
- Repeated miscarriage
- Family history of chromosome problems

PGD

To test for the presence of a specific genetic condition, a technique called polymerase chain reaction (PCR) is used. This technique has the capacity to make millions of copies of the piece of DNA being tested for and therefore allows reliable diagnosis in each of the embryos.

Who might benefit from PGD?

PGD may be beneficial to couples who are at risk of passing on a genetic condition to their children. These include couples with a family history of an inheritable genetic condition, are carriers of a genetic condition or are affected by a genetic condition. Some of the genetic conditions that PGD has been used for include:

- Cystic Fibrosis
- Huntington's disease
- Myotonic Dystrophy
- β -thalassemia
- Spinal Muscular Atrophy
- Fragile X

- Haemophilia

Many other conditions, including rare familial ones may be tested.

It is also possible to test for Chromosome Translocations. Chromosome Translocations are rearrangements of chromosome material involving two or more chromosomes. Chromosome Translocation can cause infertility and recurrent miscarriage. The majority of chromosome translocations can be detected using aCGH.

If a particular condition has not been tested before, it may be possible to “tailor make” diagnostic tests specifically for families, particularly those with rare genetic conditions.

Specific approval from The Reproductive Technology Council must be sought before couples can proceed with PGD. Approval requires a report from a Clinical Geneticist who has discussed the matter with the participants.

Considerations

Prior to commencing a PGD cycle, a suitable, accurate, diagnostic test needs to be developed (feasibility studies). There is a cost associated with the test development. Please ask the Scientific Director for the current fee. This is only required for the first PGD cycle a couple undertakes. It is possible that an accurate diagnostic test will not be able to be developed for a particular genetic disorder and therefore PGD would not be possible. This will still incur the feasibility study fee. The feasibility study can take three to six months to complete and is carried out in a genetics laboratory at Monash IVF in Melbourne.

Embryo biopsy procedures have been used extensively in major IVF clinics throughout the world since the early 1990s. Follow up studies have shown that the procedure is safe with no known adverse effects on the embryo’s potential to implant and develop normally.

It is important to understand that a genetic diagnosis might not be possible from every embryo. This may result from embryos not being of sufficient quality to biopsy and/or test results not being conclusive for some embryos.

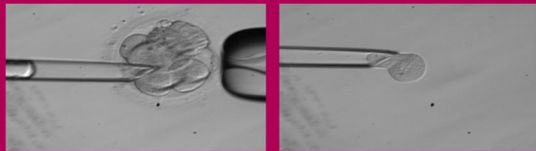
There may be a small risk that an embryo will not survive the biopsy procedure. For this reason embryos must be have at least five cells when they are biopsied.

For PGS with aCGH for chromosome screening usually only one of the developing cells are analyzed. It is possible that the cell being tested will have a different number of chromosomes to other cells of the embryos (mosaicism).

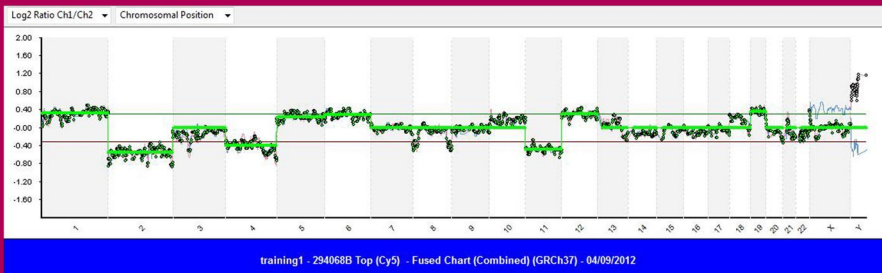
In addition, the error rate from aCGH may be 2-4%.

Both PGS and PGD require the eggs to be fertilized using the ICSI procedure (see 12.3.5).

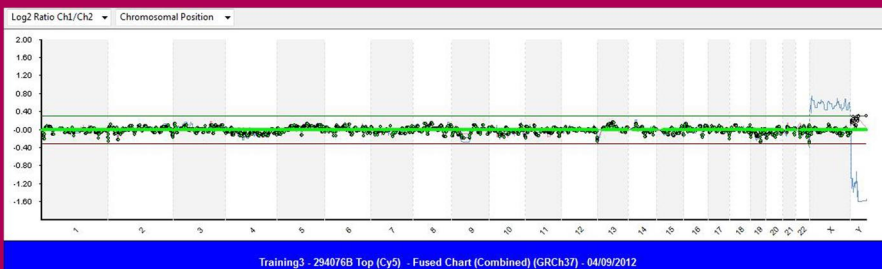
Embryo biopsy



aCGH



Only one copy of chromosomes 2, 4 and 11



Stages involved in Preimplantation Genetic Testing

Embryo Biopsy – A hole is made in the outside coating of the day 3 embryo using a laser. A fine needle is then placed through the hole to gently remove the embryonic cell(s)

Genetic Testing – for PGS a technique known as array comparative genomic hybridization (aCGH) is used. This test is also known as 24sure.

Embryo transfer – unaffected embryo(s) can be transferred on day 5. Excess normal embryos can be frozen and stored.

Data collected from international PGD centres indicates greater than 97% accuracy with PGD. Even though the diagnostic accuracy of PGD and PGS is high, prenatal diagnosis is recommended in an ensuing pregnancy.

Over 1000 children worldwide have been born following PGD with no increased risk of birth abnormalities reported compared to IVF or ICSI apparent.

If you have any questions regarding PGS / PGD please contact our Scientific Director.

Genetics and chromosomes

Our bodies are made up of millions of cells which each contain a complete copy of our individual genetic makeup (genes). The genes are tightly packaged together in the cells in the form of chromosomes. Each cell should contain 46 chromosomes (22 pairs and the two sex chromosomes). The chromosomes are numbered from 1-22 and the sex chromosomes are called X and Y. A female will have two X chromosomes and a male one X and one Y.

A chromosomal condition occurs when an individual is affected by a change in the number, size or structure of his or her chromosomes. These changes in the cells may result in problems in growth, development and functioning of the body systems.

There are two main types of chromosome changes that can occur – structural and numerical. Structural changes include chromosome translocations which occur when chromosomal material from two or more chromosomes are rearranged. These can also be detected using aCGH.

Problems associated with the number of chromosomes occur when only one or three or more copies of the particular chromosome are present in the cell. For example, in Down 's syndrome there are three copies of the number twenty one chromosome present, also known as trisomy 21.

Eggs and sperm contain 23 chromosomes, made up of 22 chromosomes and one sex chromosomes (either X for a female or Y for a male). When the egg and sperm join together at fertilization the embryo should have 46 chromosomes in its cells.

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Questions and Notes