Preimplantation Genetic Testing of Embryos (PGT-A)

Concept Fertility Centre

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Growing evidence suggests that a major factor in the failure to establish or maintain a pregnancy is when the cells in the embryo contain the wrong number of chromosomes, a condition termed aneuploidy. It has been known for some time that a significant number of human embryos have the wrong number of chromosomes (aneuploid). It is normal for a cell to contain 22 pairs of chromosomes plus the sex chromosomes, either XX for females or XY for males. Problems can arise when the embryo's cells contain too many or too few chromosomes (see back page for an expanded description).

A screening test called Next Generation Sequencing (NGS) enables scientists to screen for aneuploidy in developing embryos and confirm that the correct number of all the chromosomes are present in each embryo.

Who are eligible for PGT-A?

- Females over 35 years of age
- Those who have a history of miscarriage (>2)
- Those who have had 3 or more IVF cycles without success
- Those who have a family history of aneuploidy

How is PGT-A managed at Concept?

- Once you have decided that you would like to go ahead with PGT-A please confirm your intention by email to pgs@conceptfertility.com.au on day 1 of your cycle.
- Ovarian stimulation
- Egg collection and fertilization using IVF or ICSI.
- Embryo biopsy – removing 4-8 cells from each embryo on day 5 or 6 of development
- Embryos frozen on day 5 or 6 of development
- NGS genetic analysis
- Results available three weeks after biopsy
- Frozen embryo transfer
- It is recommended not to start a frozen embryo transfer cycle until the results of the screening are known.

Considerations

- For the embryo biopsy and screening to take place the embryos need to be an expanded blastocyst on day 5 or 6.
- It is possible that the embryo might be damaged during the biopsy procedure although this is very rare (<1%) at Concept.
- It is possible that all the embryos will have the wrong number of chromosomes and therefore no embryos would be available for transfer. Research has shown that in couples where all their embryos were affected in the first cycle, 50% of these couples had an embryo suitable for transfer in their second cycle.
- Some embryos might not develop to expanded blastocyst stage and be suitable for biopsy or transfer. This is due to another developmental problem present in the embryo that is not associated with the number of chromosomes.
- There is a 10% chance an embryo may not survive the freezing process.
- If a low number of embryos are suitable for screening it might be possible to have another egg collection procedure and then screening both sets of embryos. Concept will need to apply to the Reproductive Technology Council for approval to undergo an egg collection procedure if three or more embryos are in storage.
- There is a cost for PGT-A (not included in IVF cycle related fees) and this is not covered by Medicare or private health insurance. Please see fee schedule (12.4.2; Gold Program).

Limitations of PGT-A

- The screening results are not 100% accurate. Accuracy of NGS is 95%.
- Mosaic embryos- it is possible that the cells of the embryo are different to the biopsied trophectoderm cells and have a different set of chromosomes. NGS can detect mosaic embryos if a mixture of normal and abnormal cells are taken at the biopsy. The difficulty arises when biopsied and tested cells are normal and the cells remaining in the embryo are abnormal (eg only normal cells taken at biopsy). This is a limitation of testing only a small number of cells.
- The results might be inconclusive for some embryos, and for some embryos a result is not possible (10%).
- PGT-A cannot identify other abnormalities or birth defects that are not associated with the number of chromosomes and therefore doesn't guarantee a healthy pregnancy or birth.

Stages Involved In PGT-A

Embryo Biopsy –
Embryo biopsy procedure is performed by careful removal of a small number of trophectoderm cells that have herniated through the zona pellucida (outside shell) of an expanded blastocyst. The biopsy sample is then placed in a tube for screening and the embryo is cryopreserved.

Genetic Analysis –
For PGT-A a technique known as Next Generation Sequencing (NGS) is used.

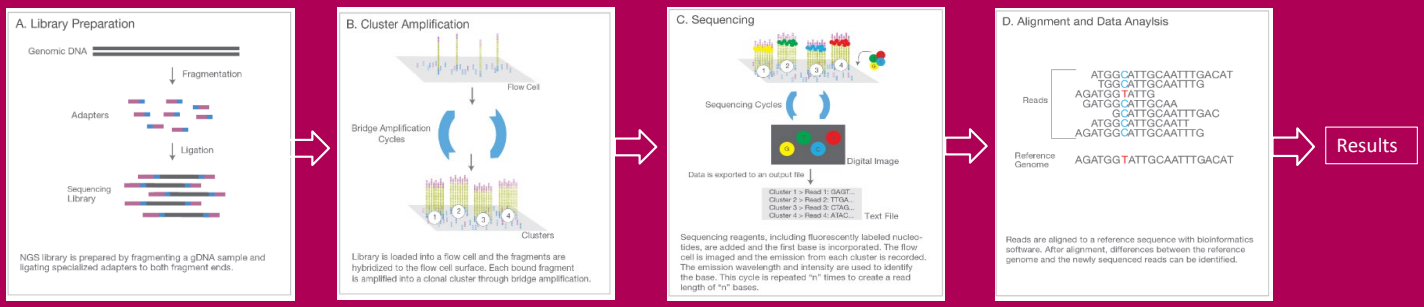
Frozen Embryo transfer cycle –
Unaffected embryo(s) can be transferred on day 5 or 6 in a frozen embryo transfer cycle. Excess normal embryos can remain frozen and stored for future use.

Embryo biopsy

Genetic Analysis

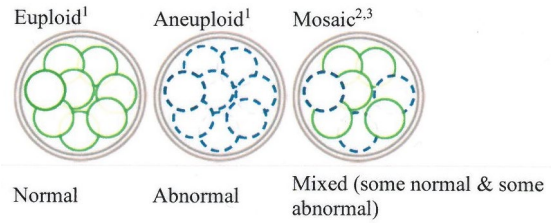
Genetic analysis for PGT-A is done using NGS.

Whole genome amplification



PGT-A Results

The following results are possible with NGS.



A euploid embryo has the correct number of chromosomes. An aneuploid embryo has a missing or extra chromosome and a mosaic embryo has a mixture of cells, some with the correct number of chromosomes and some with a missing or extra chromosome. Mosaic embryos can have implantation potential but are considered to have less chance of resulting in pregnancy than a euploid embryo. Mosaic embryos can be used but genetic counselling is recommended.

Figure 1a

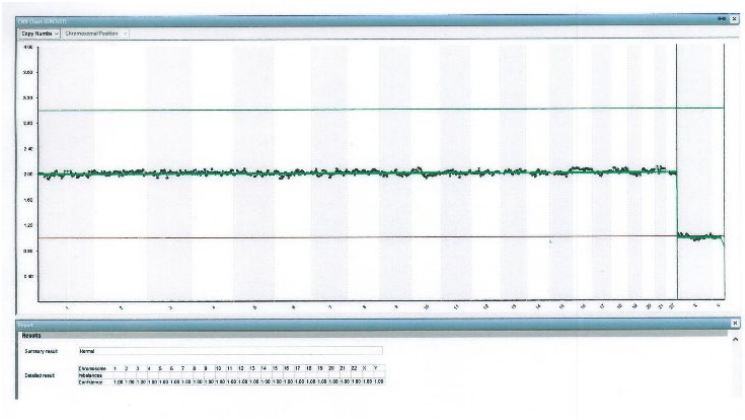


Figure 1a is an image of a NGS result from an embryo with the correct number of chromosomes (euploid). In this case there are two copies of each chromosome except the X and Y chromosome indicating a male embryo with one X and one Y chromosome.

Figure 1b

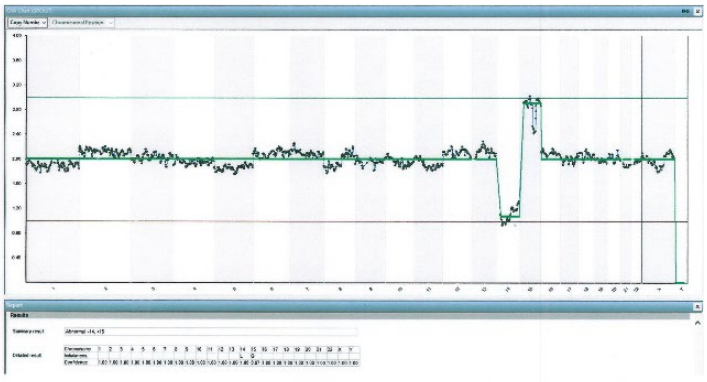


Figure 1b is an image of a NGS result from an embryo with an extra chromosome 15 and a missing chromosome 14. This embryo is called aneuploid.

Genetics and chromosomes

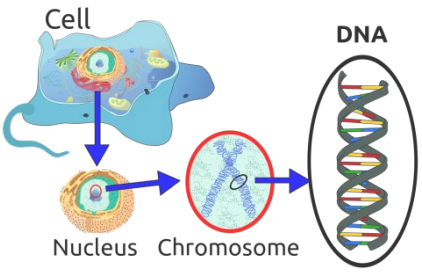
Our bodies are made up of millions of cells which each contain a complete copy of our individual genetic makeup (genes). The genes are tightly packaged together in the cells in the form of chromosomes. Each cell should contain 46 chromosomes (22 pairs and the two sex chromosomes). The chromosomes are 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. Numerical changes occur when there is a loss or gain of chromosomes (known as aneuploidy).

Human embryos have a high rate of aneuploidy and this is closely related to female age. The table below shows the frequency of normal embryos (euploid) screened on day 3 and 5 of development and female age. This provides a percentage estimation of the likely chance a woman of a particular age would have a normal embryo.

For more information please contact the Scientific Director at Concept on 9382 2388.



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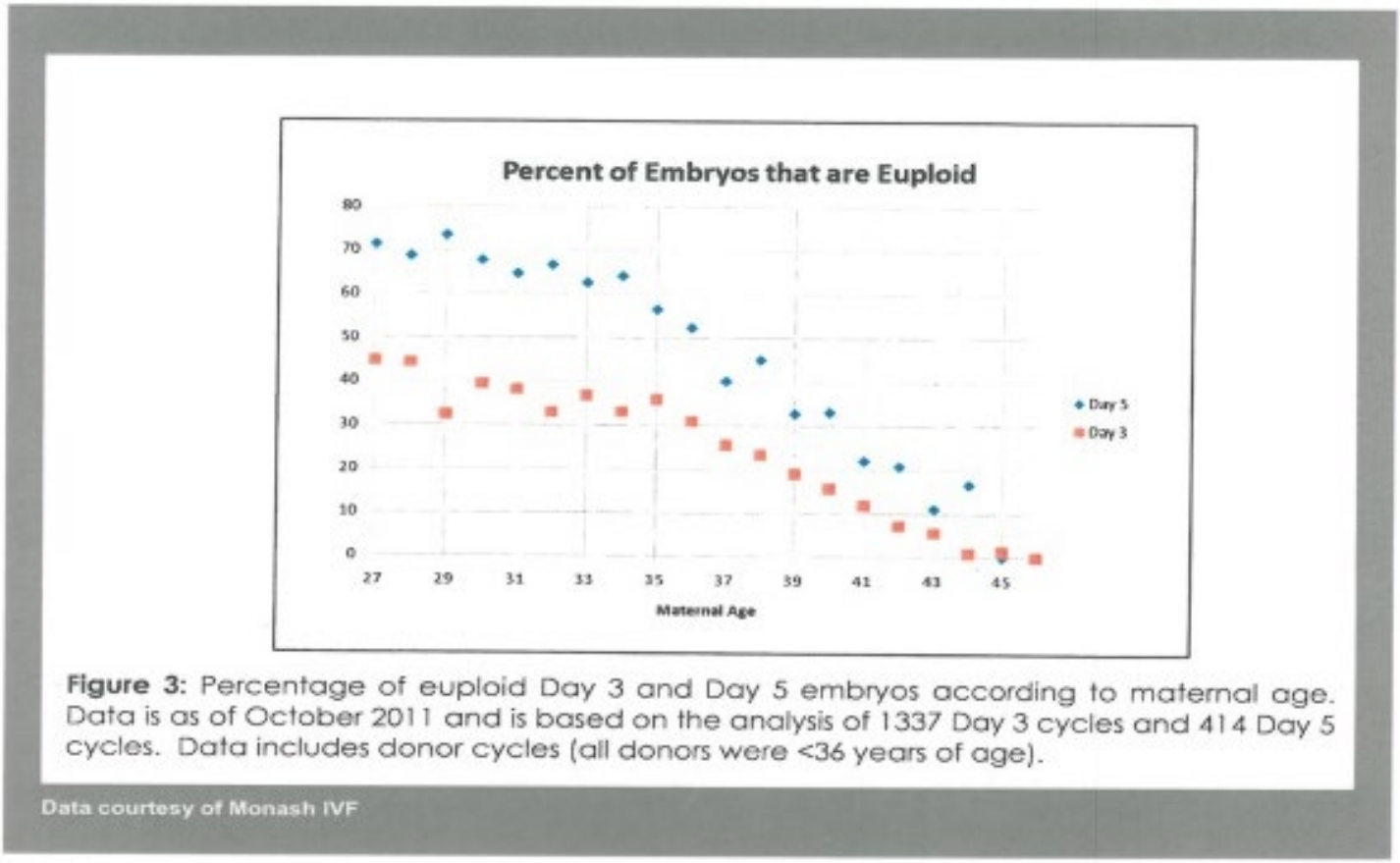

Figure 3: Percentage of euploid Day 3 and Day 5 embryos according to maternal age. Data is as of October 2011 and is based on the analysis of 1337 Day 3 cycles and 414 Day 5 cycles. Data includes donor cycles (all donors were <36 years of age).

Data courtesy of Monash IVF