Preventing genetic conditions before birth

The power of PGT

Pre-implantation genetic testing (PGT) is used to test embryos for genetic conditions, helping affected individuals to have children without those conditions. Student genetic counsellor Kirsty MacIver explains how PGT can be used as part of *in vitro* fertilisation (IVF) treatment, and explores some of the ethical issues surrounding PGT

Kirsty MacIver

There are four subcategories of pre-implantation genetic testing (PGT). PGT-M can be used to test embryos for **monogenic conditions** such as Huntington's disease, Duchenne muscular dystrophy and cystic fibrosis, where a genetic condition is caused by a variant in a specific gene. PGT-SR looks for structural rearrangements in chromosome complement such as **chromosome translocations**. PGT-A is used to detect **aneuploidy** in embryos. Some of the embryos with translocations or incorrect chromosome complement do not survive to birth, so PGT-SR and PGT-A help parents to avoid having miscarriages.

Finally, PGT-P is a newer subcategory of PGT, available commercially since 2019. It uses **polygenic risk scores** to calculate the risk of an embryo developing a **polygenic condition**. There are conflicting views on the ethical grounds of using PGT-P in clinical practice due to the limited reliability of polygenic risk scores.

PGT approval

In the National Health Service (NHS) in the UK, once a couple has been approved for PGT by their Clinical Genetics Service, they are added to a waiting list to begin the PGT process. PGT appointments are usually led by a genetic counsellor or a consultant clinical geneticist. The couple must meet the following criteria before being considered for PGT:

- The female must be under 39 years of age, because the chance of a live birth using IVF significantly declines after this age. The quality and quantity of a woman's egg reserve decreases with increasing age.
- The female must have a body mass index (BMI) between 18.5 and 30, because being underweight or overweight can cause hormonal disruption, affecting the success rate of IVF.
- The couple must both be non-smokers, because smoking by either the male or female partner significantly reduces the chances of a successful IVF cycle. Successful embryo implantation is thought to be reduced by 20% in women who smoke.
- The couple must not already have a child unaffected by the genetic condition being tested for – this is due to limited funding on the NHS.
- The female partner must have an adequate egg reserve. This ensures that the chances of a successful IVF cycle are optimal.

If the couple do not meet these criteria, they are unlikely to be eligible for PGT funded by the NHS. They may have the option to pay for a PGT cycle at a private fertility centre at a minimum cost of approximately £10 000.

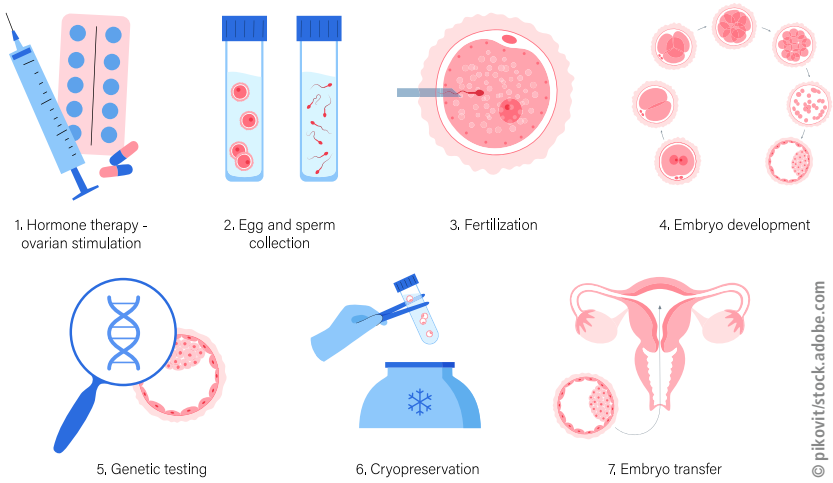

Figure 1 Step-by-step PGT process

TERMS EXPLAINED

Aneuploidy The number of chromosomes present in a cell is incorrect.

Balanced chromosome translocation All chromosomes in a cell are present but in a different orientation.

Monogenic condition A condition that is controlled by a variant in a single gene.

Polygenic condition A genetic condition that is controlled by a combination of variants in many genes.

Polygenic risk score A score given to an individual to indicate their likelihood of developing a polygenic condition based on analysis of many variants across their whole genome.

PGT process

The PGT process is normally performed as part of IVF (see Figure 1), with the following stages:

1 The female partner is usually provided with injectable follicle stimulating hormone (FSH) to self-inject for approximately 2 weeks. This encourages the ovaries to produce multiple eggs.

2 All the eggs produced are collected from both ovaries using a thin needle attached to an ultrasound probe (transvaginal ultrasound aspiration). It is a day procedure, usually carried out under sedation in a hospital by an obstetrician. A sample of the sperm from the male partner is collected.

3 The eggs are fertilised by the sperm in a laboratory, usually using a process called intracytoplasmic sperm injection (ICSI), where single sperm cells are injected directly into single mature egg cells.

4 The fertilised eggs are allowed to mature for 5–6 days until the resulting embryo is large enough for 5–10 cells to be removed for genetic testing.

5 The DNA from the embryo cells is extracted in the laboratory and tested for the gene variants causing the condition in question.

6 All of the embryos are frozen while the results are awaited.

7 Any embryos that have the disease-causing gene variant are discarded, and embryos without the gene variant can be transferred into the womb, usually a few months later.

Gene mutations are usually referred to as gene variants when working with patients in clinical practice because the word 'mutation' is thought to have negative connotations.

Only one embryo is transferred to the womb at a time, until an embryo successfully implants and results in a pregnancy. Viable embryos are stored using a freezing process called cryopreservation, using liquid nitrogen. The embryos are then thawed before implantation. The success rate of a single cycle of IVF with PGT is approximately 40%, so around 40 out of 100 women undergoing PGT will give birth at the end of the cycle.

Unfortunately, sometimes there are no unaffected embryos to transfer, the transfer fails, or none of the unaffected embryos successfully attach to the uterine lining (implantation), meaning the couple must repeat the PGT process from the start. The NHS currently funds up to three complete cycles of PGT for eligible couples until they have an unaffected child. The process is extremely emotionally and physically draining, and not all couples feel able to complete three cycles. In some cases, a couple may complete three cycles and not achieve a pregnancy.

Testing for Huntington's disease

Huntington's disease (HD) is an inherited neurological condition for which there is currently no cure. However, there has recently been a promising research trial at University College London for a treatment for HD patients, which has been shown to slow the disease by 75%. It is usually an adult-onset condition, with people experiencing symptom onset being aged between their 30s and 50s on average, which means that affected individuals are likely to have become parents before they show any symptoms.

HD is characterised by psychological symptoms, such as personality changes, memory challenges and depression, and musculoskeletal symptoms, such as uncontrollable limb movements. This progressive condition has a life expectancy of approximately 15 years from the onset of symptoms. It is inherited in an autosomal dominant manner and caused by a CAG repeat expansion on the human *HTT* gene on chromosome 4 (see Figure 2). When HD is inherited, the number of CAG repeats can

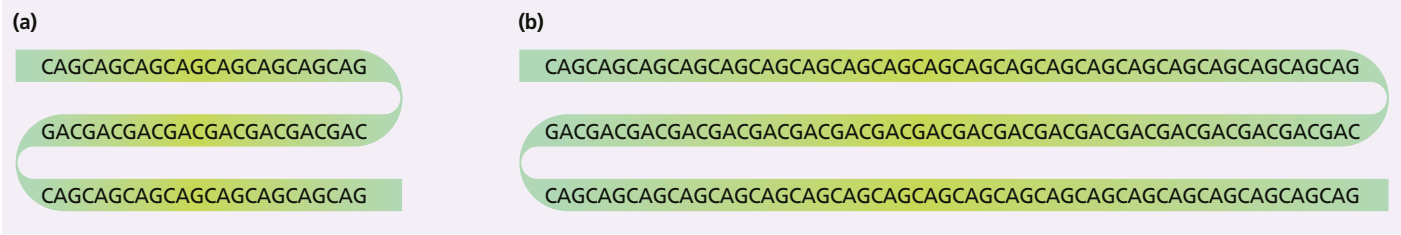

Figure 2 (a) Typical *HTT* allele (unaffected individuals): 10–35 CAG repeats. (b) HD *HTT* allele (affected individuals): >40 CAG repeats, 36–39 CAG repeats (reduced penetrance)

occasionally increase, which results in increased severity of symptoms and earlier onset of symptoms from generation to generation. This is called genetic anticipation.

An 'intermediate allele' has 27–35 CAG repeats. This means that the individual is unaffected (see Figure 2a). However, the repeat size may increase in their offspring, putting them at risk of developing HD. A 'reduced penetrance allele' has 36–39 repeats. This means that individuals with this number of repeats may develop HD in their lifetime (see Figure 2b), though it is likely that symptoms will not occur until a later age. The repeat size may increase in their offspring, putting them at risk of developing HD.

Case study: exclusion testing

Adam and Ailsa, aged 26 and 24, attended the genetics clinic. Ailsa's mother, Angela, is in her 60s and is affected by HD (see Figure 3a). Her symptoms are quite advanced and sadly, she is deteriorating quickly. Ailsa is a part-time carer for her mother. Ailsa has a 50% chance of also having HD due to its autosomal dominant inheritance pattern (see Figure 3b) but does not wish to know her genetic status. The idea of developing symptoms like her mother scares her and she would rather not know if she was going to develop them in the future.

Adam and Ailsa would like to have a family of their own, although they have both agreed that they would not want to give birth to a baby at risk of HD. Exclusion testing can be performed with PGT to allow Adam and Ailsa to have a baby at low risk of HD, without revealing Ailsa's genetic status.

Exclusion testing is carried out by taking blood samples from Ailsa and her mother, Angela, and following the inheritance of the grand maternal (Angela's) chromosomes to determine a high-risk embryo (it has inherited one of Angela's chromosome 4s) or low-risk embryo (it has not inherited either of Angela's chromosomes 4s) (see Figure 4).

Exclusion testing with PGT allowed Ailsa to give birth to a baby at low risk of HD, without

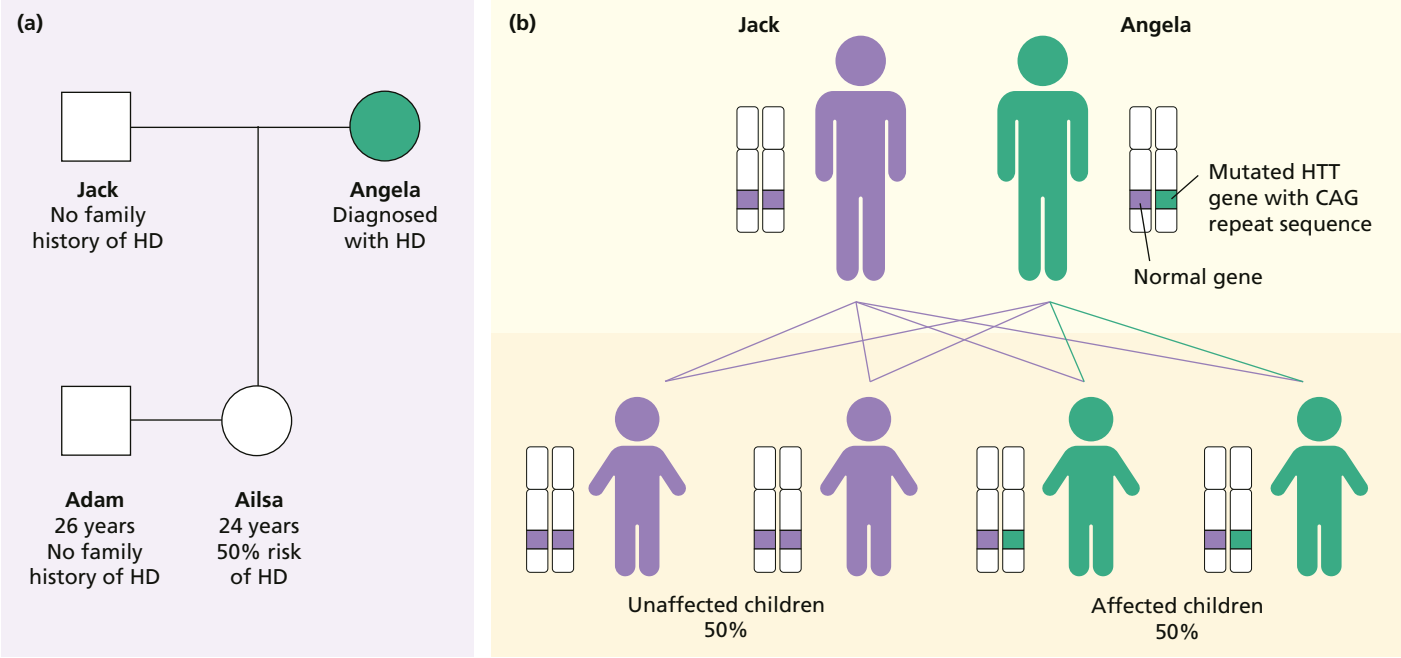

Figure 3 (a) Family tree depicting Ailsa's family history of Huntington's disease (b) Ailsa's risk of developing HD is 50% due to the autosomal dominant inheritance pattern

revealing her own genetic status. The risk is never zero, as there is always a small risk of a new disease-causing variant occurring. The embryos in this case are not directly tested for the CAG repeat to avoid revealing Ailsa's genetic status. Instead, embryos are regarded high risk if they have inherited a chromosome from Angela, Ailsa's mother. These 'high-risk' embryos are discarded.

As only one of Angela's chromosomes is affected with the CAG repeat, this means potentially discarding healthy embryos. Some individuals may argue that this form of testing is unethical due to the high risk of discarding healthy embryos. However, the counterargument for this is that Ailsa has the right to have children and to make her own informed decisions regarding her health.

Is PGT right for everyone?

Bioethics is the study of ethical dilemmas emerging in biology and clinical practice. Due to the fact that PGT involves the discarding of live and viable embryos, there are differing opinions regarding when it is ethical to offer PGT. There are many scenarios where there are differing ethical opinions as to whether PGT should be used. Let us look at some examples to provide points for thought and discussion. In the world of ethics, there is rarely a clear right or wrong answer and there tend to be credible arguments for both sides of a discussion.

Cancer predisposition genes

One of the most common reasons for adults attending a genetics clinic is due to a significant family history of cancer. There are many gene variants that increase the risk of various types of cancer. The most well-known cancer predisposition genes are probably the BRCA1 and BRCA2 variants, which increase the risk of breast and ovarian cancer in women. These gene variants are not thought to increase the risk of cancer before adulthood. For this reason, childhood testing is not offered for these types of gene variants.

However, for adults who know they are a carrier of one of these variants, PGT is available. Some parents feel that they would like to be guaranteed to have a baby without a cancer predisposition gene to avoid them having a greater health risk when they are adults. The contradicting argument is that this kind of PGT results in discarding embryos that would likely grow into healthy babies. In 18 years' time, healthcare may have advanced, and more options may be available for individuals with these gene variants.

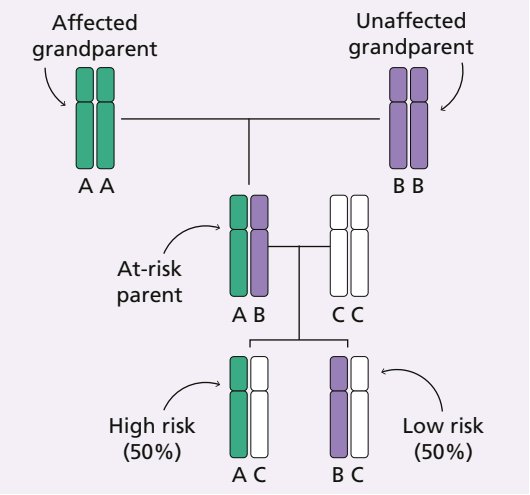

Figure 4 Exclusion testing can identify 'high-risk' and 'low-risk' embryos

Deafness

Another topic of controversy around PGT is genetic predisposition to deafness. The word deaf with a lower-case 'd' refers to the deaf phenotype, whereas Deaf with an upper-case 'D' refers to a cultural identity and the Deaf community. Many who identify as Deaf do not see deafness as a disadvantage. Some Deaf people have requested PGT to select for deafness to allow for their child to be a part of their community, have the same identity and communicate using British Sign Language. They have argued that having a hearing child would exclude that child from their community.

Topic for discussion

- What do you think about offering PGT in the scenarios discussed in this article?

RESOURCES

Pre-implantation genetic testing: **https://tinyurl.com/preimplantation-testing**

Polygenic risk scores: how useful are they? **https://tinyurl.com/polygenic-risk-scores**

Exclusion testing in pregnancy for Huntington's disease: **https://tinyurl.com/exclusion-testing**

Huntington's Disease Association: **www.hda.org.uk/**

Huntington's disease successfully treated for the first time: **https://tinyurl.com/BBC-Huntingtons**

Addressing ethical issues related to prenatal diagnostic procedures: **https://tinyurl.com/ethical-issues-prenatal**

Article: is it ever morally permissible to select for deafness in one's child? **https://tinyurl.com/select-for-deafness**

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