A Guide to
Pre-implantation
Genetic Diagnosis

By Ailsa Taylor

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Executive Summary

Since 1989 it has been possible to create embryos, by mixing sperm and eggs in the laboratory, and then to test them for certain genetic and chromosomal conditions, using a technique called Pre-implantation Genetic Diagnosis (PGD). When PGD first became available, it was used primarily by couples known to be at high risk of passing on a serious genetic disorder to their children. But in more recent years a number of unforeseen uses of PGD have emerged, making headlines and attracting a firestorm of responses from both scientists and the public.

For example, several couples worldwide have used PGD to conceive tissue matched babies who can donate umbilical cord blood to help save the lives of sick siblings – so-called 'saviour siblings'. Other unforeseen uses of PGD include sex selection for non-medical reasons and testing for diseases that do not appear until late adulthood, or similarly 'predispositions' to disease that may never result in illness. In addition to these new uses of PGD, some infertility experts have suggested that the embryos of all patients undergoing *in vitro* fertilisation (IVF) treatment should be routinely screened for chromosomal abnormalities, using a variation of PGD called Preimplantation Genetic Screening (PGS). But given the invasive nature of PGS, opponents argue that in most cases infertile patients stand a better chance of a live birth without any additional tests on their IVF embryos.

While PGD represents a revolutionary step towards the goal of increasing reproductive choice, it is also exists as a powerful force demanding carefully considered regulatory and legal frameworks, with input from a wide range of experts including ethicists, medical professionals, patients and the general public.

What follows is intended as a simple guide to pre-implantation genetic diagnosis aimed at highlighting the relevant procedures and technologies behind PGD, as well as its past, present and future applications. By shedding light on some of the important ethical and legal dilemmas raised by this technology, this booklet provides information for those who may wish to join the debate over PGD, who need to make use of PGD themselves, or who just want to learn more about the subject.

Introduction

Over recent decades our understanding of the genetic basis of human disease has increased dramatically, enabling us to pinpoint the causes of many inherited conditions right down at the level of the DNA of the genes. Along with the development of powerful techniques to detect the specific gene mutations that cause serious diseases such as cystic fibrosis, Duchenne muscular dystrophy or thalassaemia, this knowledge has led to many new diagnostic and predictive genetic tests. But knowing what causes a genetic condition does not necessarily mean that we better know how to treat it. Without the cures to match, many couples at risk of having a child with a serious genetic disorder have, in the past, been left with an extremely difficult decision to make. Should they risk bringing an unhealthy child into the world or decide not to have children at all? But today, the development of new reproductive technologies has increased the options available to couples in this difficult situation.

One such technology – a procedure known as Prenatal Diagnosis (PND) – gives couples the option of choosing to terminate a pregnancy which tests positive for a particular genetic disorder. But making a choice over whether or not to terminate a pregnancy can be a very difficult decision in itself and one which, whether it be for moral, religious or personal reasons, many couples find unacceptable. The development of Pre-implantation Genetic Diagnosis (PGD) provides another option for some of these families, one that allows couples at increased risk of passing on a genetic disorder to their children to start their pregnancy with the same chance of having a healthy baby as anyone else.

PGD is a technique which brings together IVF and genetic testing, enabling couples to create embryos in the laboratory by mixing eggs and sperm, and then carry out genetic tests on them, transferring only those embryos free of a specific genetic defect to the womb.

IVF success rates (that is the percentage of cycles which result in a live birth) currently average 21.6% (HFEA, 2007) and PGD rates are probably similar or lower than IVF as a whole. Moreover, the costs involved with PGD are considerable, and in most countries the entire expense is met by the patients themselves. This may in part

help to explain why PGD is currently not in wide use. These two factors may help to explain why PGD is not likely to become widely used for non-essential reasons. The primary objective of PGD has always been to avoid harm to the unborn child and in the beginning it was solely used by couples at risk from passing on a serious genetic disorder to their children. Nonetheless, the use of PGD is expanding, creating new ethical and legal dilemmas in need of careful scrutiny and regulation.

Pre-implantation Genetic Diagnosis

What is PGD?

Pre-implantation Genetic Diagnosis (PGD) brings together two areas of science: in vitro fertilisation (IVF) – originally developed to treat infertility – and genetic testing. IVF involves extracting eggs from the woman, obtaining sperm from her partner and mixing them together in a glass dish so that fertilisation can take place outside of the mother's body. When carried out for PGD, a variation of IVF called intracytoplasmic sperm injection (ICSI) is generally used, where a single sperm is injected into the egg. This ensures the sample isn't contaminated by non-embryo DNA, which could make the risk of a wrong diagnosis higher. For infertile couples, any resulting embryos would be checked to make sure they are developing normally and then one, or occasionally two, would be transferred back into the mother's womb in the hope that a pregnancy will result. But in PGD this checking process goes a step further to look at the genetic make up of the embryo.

In PGD the embryos are allowed to develop in the laboratory for three days, during which time they undergo three cell divisions, until they consist of around eight cells. At this stage in the embryo's development every cell is identical and has the ability to develop into any tissue in the body, a state known as 'totipotence'. As a result, it is possible to ascertain the genetic make up of embryos created in this way by using a fine glass tube to remove one or two cells from the embryo, without affecting its normal development, in a process known as an 'embryo biopsy'.

The biopsied cells are tested in one of two ways, depending on the type of genetic abnormality (see fig.1). If the genetic abnormality is a mutation in a single gene, the relevant section of DNA from them must first be extracted and copied many times so

there is enough to reliably test for a mutation in the laboratory. This is done using the polymerase chain reaction (PCR), a DNA-amplification technique which, although it has been in routine use for the past fifteen years, is still technically demanding when carried out on a single cell.

To test for chromosomal abnormalities or to determine the sex of an embryo, another technique called fluorescent *in situ* hybridisation (FISH) is used. FISH uses fluorescent 'tags' to look directly at the chromosome complement of a cell e.g. to detect the Y-chromosome in sex determination or to detect chromosomal abnormalities.

Fig 1: Methods for detecting gene and chromosome abnormalities in PGD

Fluorescent In Situ Hybridization (FISH)

Fluorescently-labelled pieces of DNA are used to detect specific genes, chromosome segments or chromosomes, in the cell when examined under a special microscope.
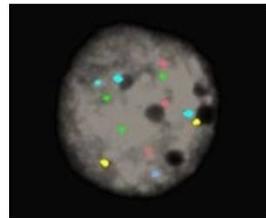
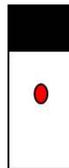### Embryo Biopsy

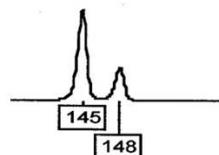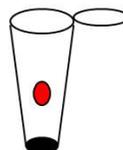A fine glass tube is used to remove one or two cells from the embryo, without affecting its normal development.

Polymerase Chain Reaction (PCR)

A technique for making millions of copies of a specific DNA sequence, used to detect a single letter gene change in the DNA of the cell.

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How is PGD used?

Single-Gene Disorders

Originally PGD was developed to help parents avoid passing on a known genetic disorder to their children, without going through the multiple terminations often encountered following prenatal diagnosis (PND). For the first time, PGD allowed couples to know their baby would not have the genetic disorder, even before the pregnancy began.

The nature of the technique (see 'embryo selection') means that generally, only those at risk from passing on genetic disorders caused by a *known* mutation in a single gene (e.g. cystic fibrosis) or where the disorder only affects males (e.g. haemophilia) are suitable candidates for PGD. A new technique called Preimplantation Genetic Haplotyping (PGH) means that PGD can also now be used in some families where the faulty gene has been pinpointed, but the exact mutation remains unknown (for details see below).

Chromosomal Abnormalities

Sometimes birth defects are caused, not by a tiny mutation in a single gene, but by a big rearrangement of the chromosomes called translocations, in which parts of two different chromosomes have switched places. A person may have a 'balanced' translocation and be healthy, but have a high risk of having a child with an 'unbalanced' translocation causing either recurrent miscarriage or problems with development of the fetus. PGD can be used to test which type of translocation is carried by the embryo.

BOX 1: Could embryo screening improve pregnancy rates?

Another type of embryo test, known as preimplantation genetic screening (PGS) or aneuploidy screening, allows the chromosomes of an embryo - rather than its particular genes - to be studied in order to establish whether there is the right number. 'Aneuploidy', a condition more common in older women embarking on pregnancy, is the situation where an embryo contains the wrong number of chromosomes in each cell - a state which normally prevents embryos from

developing. It can also cause miscarriage or chromosomal conditions such as Down syndrome and is thought to be a likely cause of much 'unexplained infertility'. In PGS, embryos found to have the wrong number of chromosomes would not be implanted into the womb, thus boosting the chances of having a successful pregnancy.

The Human Fertilisation and Embryology Authority (HFEA) first licensed PGS in 2002, and the first reported UK birth following the use of this technique was in 2003. However, there is continuing disagreement over the utility and efficacy of PGS, with critics saying that its benefits are unproven (Ogilvie 2008), while supporters say that it improves the chances of a successful pregnancy in certain groups of patients.

One of the concerns over PGS is that it is inevitable that a significant proportion of embryos tested will produce false positive test results. This is because, to perform an embryo biopsy without affecting the viability of the embryo, it is necessary to test the embryos at a stage where cells are likely to be at their chromosomally most non-uniform (mosaic) - contradicting the principle that the genetic makeup of the cell sampled is representative of the whole embryo. In other words, it could be that at this early stage, many embryos may have one or two cells with the incorrect number of chromosomes – but these cells may be lost as development proceeds – scientists just don't know. Another major concern is that the embryo may be otherwise damaged during embryo biopsy, reducing the likelihood of a successful pregnancy.

Indeed some more recent studies looking at the efficacy of PGS have found that both the pregnancy and live birth rates were lower for IVF babies born after PGS, compared to those born without this added treatment (Mastenbroek, 2007). While not all chromosomal abnormalities can be detected using PGS - meaning that an apparently 'normal' embryo may still harbour serious genetic errors - such findings highlight the need for further research into the benefit of PGS among specific groups of women, including older women, couples who have had unexplained recurrent miscarriages and those who have experienced repeated IVF failure.

Genetic Disorders where the gene but not the mutation is known

Until recently, one of the main limitations of PGD was that it could only be used where the family's specific mutation is known, or for conditions that are X-linked -

usually only affecting boys – which can be avoided by selecting only female embryos. But a relatively new technique known as Preimplantation Genetic Haplotyping (PGH) is helping to solve this problem, and is also increasingly used as a more reliable alternative to PGD in some centres. Rather than looking at the genetic mutation itself, PGH looks at a set of surrounding DNA 'markers' that can distinguish the chromosome with the faulty version of the gene from the one carrying the healthy version. The chances of a wrong diagnosis are thought to be much lower with PGH because the test looks at several different DNA sequences, instead of just one (the mutation).

One of the advantages of PGH is therefore that it can be offered to families at risk from passing on rare mutations which have yet to be identified, as well as those with more common previously identified mutations. It is also useful for families affected by an X-linked disease – those which only affect boys – as it allows doctors to distinguish affected male embryos from unaffected ones – potentially increasing the number of healthy embryos that can be transferred to the womb and removing the need to select only females.

'Saviour Siblings'

For a handful of cases to date, PGD has been used in order to have a child who is a tissue match for an existing sick sibling who requires a blood stem cell transplant – a so-called 'saviour sibling'. This is done by using PGD to rule out diseased embryos and then testing the remaining embryos to select those with the same tissue-type genes as the sick sibling. The aim is to match the stem cell recipient's antigens – proteins found on the surfaces of cells which act to stop the immune system from attacking the body's own cells.

When the child is born stem cells may harmlessly be taken from the baby's umbilical cord, which would usually be discarded along with the placenta, and used to repopulate the bone marrow of the sick sibling. If successful this procedure can effectively provide a cure for children affected by one of several life-threatening blood disorders, including leukaemia, Diamond-Blackfan anaemia, Fanconi anaemia, beta thalassaemia major or severe combined immunodeficiency syndrome.

BOX2: Adam Nash – the world's first 'saviour sibling'

In October 2000 US couple Jack and Lisa Nash became the first to use PGD to conceive a son who was not only free of a rare inherited disease, but also a tissue match for his sick sister, Molly. Molly Nash had Fanconi's anaemia, a life-threatening condition with a range of symptoms, including a lack of healthy blood stem cells in the bone marrow. Mr and Mrs Nash wanted more children but know they had a 1 in 4 chance of conceiving another affected child. Using PGD, the doctors found one disease-free embryo that was potentially able to provide a matched transplant for Molly and which was healthy enough to transfer to Mrs Nash's womb. Adam Nash was born on 29th August and one month later blood stem cells from his umbilical cord were successfully transplanted into Molly, effectively curing her from her condition.

What does PGD involve?

Step 1: Stimulation of the Ovaries

Normally, a woman releases one egg per menstrual cycle, usually around two weeks after her last period. In IVF treatment, the hormones which naturally cause a woman to release eggs from her ovaries are first suppressed in order to make her more sensitive to the ovary stimulating drugs - hormone injections which cause several eggs to ripen in her ovaries at once – which are given subsequently.

As with any medical treatment, there are potential physical side effects. Mood swings, headaches, night sweats and hot flushes are all associated with the drugs used for ovary suppression and bloatedness, nausea, tender breasts and feeling emotional with those used for ovary stimulation.

Step 2: Monitoring egg development

Following a course of hormone injections, the woman's ovaries are monitored closely using ultrasound – the scans used to check on the baby's development during a normal pregnancy – and sometimes blood tests. When the ripening eggs have reached the right size, the woman is given a final injection which triggers the eggs to reach full maturity.

Step 3: Egg collection

Around 34-36 hours after the final hormone injection, the woman's eggs are ready to be collected. The woman is put under deep sedation and, using ultrasound to locate the woman's ovaries, the doctor gently inserts a fine needle up through the vagina and through the vaginal wall where it is used to collect the mature eggs from around the ovaries. A sample of sperm is also produced by the male partner at this stage.

Step 4: IVF Fertilisation

About 4-6 hours after the eggs and sperm are collected they are mixed together and placed in an incubator in order to start off the process of fertilisation (see fig.2). When IVF is being carried out for PGD, a single sperm is generally used to fertilise an egg, to avoid contamination problems. Any resulting embryos – fertilised eggs which

Fig. 2: In vitro fertilisation (IVF)
In IVF, eggs are harvested from the woman's ovary and fertilised in the laboratory with sperm. In PGD, the embryos are also checked to ensure that only those unaffected by a particular genetic condition are transferred to the uterus.
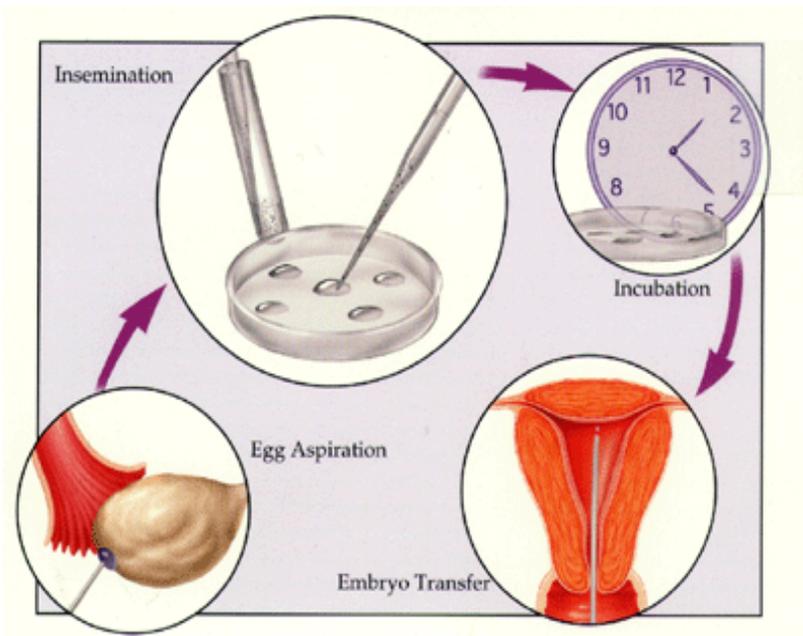
have begun dividing - are allowed to develop in the laboratory for 2-3days.

Step 5: PGD and Embryo Transfer

A fine glass tube is used to remove a single cell from those embryos which, three days after fertilisation, have reached the 8-cell stage (see fig 3). Each of the removed cells reflects the genetic makeup of the embryo from which they came. This process – known as an embryo biopsy – does not harm the normal development of the cell. A genetic test is carried out on each of the biopsied cells to determine which are free from the genetic abnormality being tested for.

Although in the past up to three embryos were transferred, today just one of the selected embryos is implanted back into the womb in the hope that a pregnancy will result. The couple are given the choice of either, freezing the remaining embryos for
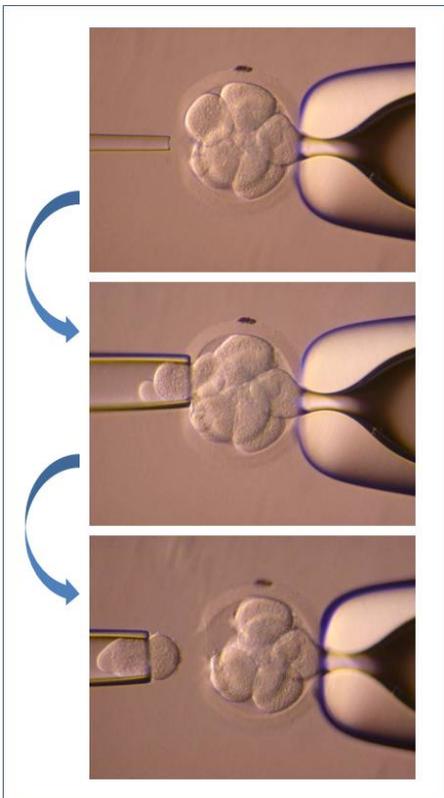

Fig.3: Human IVF embryo during embryo biopsy for pre-implantation genetic testing
A pipette (right) holds an eight-celled embryo (centre) produced by *in vitro* fertilisation (IVF) in the laboratory. First the 'shell' around the embryo is punctured with an acid solution (top left) Then a small pipette draws off one cell from the embryo (bottom left).

storage, donating them to research or leaving them to degenerate in the laboratory, a process which usually takes place naturally within a few hours.

Step 6: Implantation & Pregnancy Test

In a successful round of PGD, the transferred embryo will implant in the womb of the female partner resulting in a pregnancy. The chances of this happening can be improved by giving the woman a daily dose of progesterone, a hormone which thickens the lining of the womb. Implantation usually takes place between the fifth and seventh day after fertilisation, with a pregnancy test being taken after fourteen days.

Is PGD safe?

Concerns over the safety of PGD revolve mostly around the processes involved, namely IVF - creating embryos in the lab, and embryo biopsy - removing cells from early embryos. Although controversial, there is some evidence to suggest that babies born after IVF have a lower birth weight and are more prone to premature birth (Schieve, 2002; Hansen 2002). Twins and triplets, whether conceived naturally or using assisted reproduction techniques, are known to face a higher risk of birth defects than single babies, so these factors alone could explain these abnormalities. Yet some studies looking at IVF singletons and twins separately challenge this assumption.

A British study found that IVF babies are twice as likely to be born prematurely before 37 weeks of gestation, and three times more likely to be born before 32 weeks (Helmerhorst et al., 2004). The researchers also found that single IVF babies were three times more likely to have a very low birth weight and were slightly more likely to encounter birth complications. While the arrival of early or lower weight babies could be attributed to the original fertility problems or advanced maternal age, on current evidence it is not possible to rule out a potential link between assisted reproduction techniques, like PGD, and birth defects.

On the other hand other large-scale studies have found no such trend. One such study looked at a group of 754 babies born after a total of 4,748 PGD attempts over a 12-year period at the world's three largest PGD centres (Verlinsky et al, 2004).

Although the researchers found there was a small increase in some conditions, e.g. a 0.4% increase in Down syndrome or spina bifida and 2-4% increase in cleft palate. However, given that maternal age is linked to birth defects, one explanation for these small increases might be that mothers undergoing PGD tend to be older than women conceiving normally.

While there is no robust evidence to suggest that IVF increases the incidence of major birth defects, cancers or problems in psychological or emotional development, some studies have linked IVF to a slightly increased risk of some rare genetic conditions caused by faulty 'genetic imprinting', such as Beckwith Wiedemann syndrome (BWS). Genetic imprinting is the process by which certain genes are normally switched off during early embryo development, according to whether they were inherited from the father or mother. BWS is one of several imprinting disorders, which are all caused by disruptions to imprinted genes or to the imprinting process itself. American researchers at Johns Hopkins University and the University of Washington first identified a possible link between IVF treatment and BWS in 2003. Two other groups of researchers later confirmed a link between assisted reproduction techniques and an increased risk of BWS, in studies of UK (Maher, 2003) and Australian (Halliday, 2004) BWS patients. Other studies have suggested a link between assisted reproduction techniques and other rare genetic conditions. Again advanced maternal age and the original fertility problems could be one alternative explanation for these links.

Most of the data collected so far about babies born following PGD relate to the outcome at birth, meaning that the longer-term outcomes of babies born following PGD are still unknown. One recent study found that carrying out genetic tests on the developing embryos had no effect on the health of the resulting babies (BioNews, 2007). The researchers monitored the health of over 500 babies born after PGD or PGS over two years and found that at 3.6%, the rate of major birth defects in the PGD babies was no higher than that in the IVF or ICSI groups studied. Although these results are reassuring, experts have highlighted that it will take several more decades to look at the longer term outcomes of PGD given that the oldest PGD children are now 18.

Nonetheless a few longer term studies are on the horizon. One currently underway at Guy's and St. Thomas Hospital in London is monitoring the health of 120 babies born through PGD for the first eight years of their lives (Lashwood et al. 2007). Some early findings from this study have indicated a slight increase in the incidence of certain birth defects, ranging from relatively common conditions, such as developmental delay, birthmarks and undescended testes, to comparatively rare ones, such as skeletal abnormalities and the lazy eye syndrome.

But given that the frequency of such abnormalities among babies conceived naturally may be as high as 15% for minor abnormalities and 5% for major abnormalities (Stephenson & Hall, 2006), these results are by no means cause for alarm. Firstly, these babies have been examined more thoroughly than normal, so without a non-PGD group of babies for comparison, it is difficult to say whether the results give an accurate picture. Secondly, the study group is relatively small considering the relatively low background frequency of birth defects among natural births, and so larger collaborative studies will be needed to obtain any conclusive data.

It is estimated that only a couple of thousand babies around the world have been born following PGD and the evidence so far suggests that PGD is no more risky than other forms of assisted reproduction. However most of the data collected so far about babies born following PGD relate to the outcome at birth, highlighting the need for long-term follow-up of PGD babies, as well as a combined research effort to carry out further studies into the safety of PGD.

Are there any alternatives?

Today PGD remains a technically challenging and labour intensive procedure which is generally only used as a last resort for couples who feel they have no other option. Nevertheless, there are some alternatives for couples at risk of transmitting genetic disorders to their children.

One alternative, known as Pre-natal Diagnosis (PND), involves carrying out a genetic test during the pregnancy. This is done by obtaining a small amount of material from the fetus using either 'chorionic villus sampling' (CVS) – removing a few cells from the placenta – or amniocentesis – removing a small amount of the cell-containing fluid

that surrounds the fetus. DNA is extracted from the material which can be testing in the lab for a number of known genetic conditions, including genetic mutations and chromosomal abnormalities. Both techniques carry some risk as they involve inserting a needle into the womb, a procedure which causes around 1% of women to miscarry.

If, through PND, a couple discover that the fetus is affected, they may wish to terminate the pregnancy and in the UK, are permitted to do so up to 24 weeks of gestation and also beyond that point if the fetus is affected by a serious medical condition or if the mother's health is at risk.

Deciding whether to terminate a pregnancy is an extremely difficult decision to make. Couples are counselled by a medical team about the implications of both raising an affected child or instead terminating the pregnancy and are encouraged to consider both outcomes extremely carefully, however the final decision is left entirely in the hands of the couple in question. Whether for moral, religious or personal reasons, many couples find the idea of terminating a pregnancy unacceptable and are thus unsuitable candidates for PND.

Another alternative to PGD is to use donor eggs or sperm in place of whichever individual is at risk of passing on the genetic disorder. Although the couple may not be infertile, embryos are usually created in the lab using IVF as this allows embryos to be frozen for future use either in the case where the treatment fails to result in a pregnancy or where families wish to have a second child using the same donated eggs or sperm at a later date.

A child usually inherits half of its genetic material from its mother and half from its father - so perhaps the most obvious disadvantage of using donor eggs or sperm is that only one of the parents is genetically related to the child. However, many couples have an intrinsic desire to have children that are genetically related to them and therefore find this unsatisfactory.

Furthermore some couples feel that, by using IVF to create embryos in the lab and then implanting them artificially into the womb, they are somehow missing out on the biological relationship that a mother normally has with a child.

For couples who find the idea of terminating a pregnancy or carrying a child that is not 100% their own unacceptable, the only remaining alternatives to PGD at present are adoption or voluntary childlessness.

History of PGD

PGD was thought about for many years before it became possible. Nevertheless there were two main advances in science necessary to make it a reality.

Firstly, there needed to be a way of creating embryos outside of the woman's body so that they could be screened for genetic defects. During the 1970's scientists perfected the technique of *In vitro* fertilisation (IVF) (sometimes referred to as 'test-tube' fertilisation despite being carried out in a glass dish) which involves removing the eggs from a woman's body, fertilizing them with sperm in the laboratory, and then returning the fertilized embryo to the mother's womb to continue developing into a healthy baby. The first IVF baby – Louise Brown – was born at 11.47pm on July 25 1978. Her birth made headlines around the world and was the result of twelve years of research by the scientist, Robert Edwards, and the late obstetrician, Patrick Steptoe.

Both scientists realised that their technique could potentially be used to genetically test embryos before implanting them in the womb – the theory behind PGD – but were unable to achieve this in the absence of an effective method for amplifying a specific section of DNA in the single cell removed from a developing embryo.

In 1986 along came just such a scientific breakthrough - the so-called 'polymerase chain reaction' (Saiki R. et al, 1986). PCR is a laboratory technique for multiplying short sequences of DNA by copying them many times over, so that there is enough material for further tests. In terms of PGD, this technique provided a means of amplifying specific DNA fragments from inside a single cell extracted from a developing embryo, such that it could be tested for genetic faults in the lab.

Secondly there needed to be genetic tests available for the conditions which would to be tested for. By the turn of the millennium scientists had managed to pinpoint the cause of many of the conditions caused by a change in a single gene (for example,

cystic fibrosis) and to develop genetic tests capable of revealing the exact gene change responsible.

But still there was another hurdle to overcome before PGD became possible – how to remove a single cell from an embryo without damaging it - a procedure known as 'embryo biopsy'.

Alan Handyside and Robert Winston were amongst the first two scientists to solve this problem and ultimately to bring PGD into the clinical arena. With colleagues it took them four painstaking years to perfect the techniques, using PCR and embryo biopsy, into a format which they felt was safe enough to produce a live baby. In 1989 the world's first babies selected to be free from a genetic condition were born.

Regulation of PGD

Fears that the use of PGD might get 'out of control' have led to its tight regulation in the UK and abroad. Moral objections to the destruction of human embryos coupled with concerns over the potential use of PGD to select embryos for non-medical traits have triggered some countries to ban PGD outright, including Austria, Germany, Switzerland and Italy. Even within those countries where it is permitted, its use is limited to detecting serious medical conditions.

Internationally there are two main approaches to the regulation of PGD: statutory legislation - as in Italy, Germany, Switzerland, France and Canada – or professionally binding guidelines published by scientific societies and ethics committees – as in Greece, Portugal, the Republic of Ireland and the USA (Jones H.W. et al, 2004; Krones T. Et al., 2004). But in the UK a unique approach is taken.

The UK parliament created a regulatory body called the Human Fertilisation and Embryology Authority (HFEA) that is responsible for overseeing all fertility treatment and embryo research. Fertility centres wishing to carry out PGD have to submit an application for each new test they wish to carry out. This is reviewed by the HFEA's licensing committee on a case-by-case basis and judged on the basis of statutory guidelines, taking into consideration factors such as the welfare of the child and any other child who might be affected by their birth, the seriousness of the condition, the

level of risk of having an affected child, and the reproductive history of those seeking treatment.

Although each licence can take many months to be issued - a time delay which many patients and practitioners find bureaucratic and frustrating - there are some advantages to this approach. Firstly, having a universal regulator guarantees that the quality of the service is the same for everyone and also that the process by which licenses are procured is both accountable and transparent. Secondly, it raises the prospect of involving the public in decisions over how reproductive technologies should be regulated, and indeed the HFEA has hosted a number of public consultations aimed at informing guidelines for novel uses of PGD. Finally, given the fast-paced nature of reproductive medicine, it means that regulatory guidelines are flexible enough to respond to unforeseen uses of reproductive technologies, without necessitating the drawn out process of making changes to the law.

For those considering seeking PGD abroad, it is worth noting that the regulations, professional standards and accreditation requirements differ markedly across Europe. This issue was highlighted in a recent study examining the provision and quality assurance of PGD services in 53 centres across Europe, which found that only a third of centres surveyed had achieved or are preparing for accreditation (Corveleyn et al. 2008), and also in this year's report from the European Society of Human Reproduction and Embryology (ESHRE) PGD consortium, a task force set up in 1997 to monitor the provision of PGD and PGS services in Europe (Harper et al, 2008). Both groups of researchers have called for improvement in quality assurance and the latter has set up a dedicated working group to investigate laboratory accreditation, which is now mandatory in many laboratories. It is widely anticipated that new international standards currently entering into force, such as the European Tissue Directive, will force the issue of accreditation further, bringing important improvements in the quality management of PGD services throughout Europe (Corveleyn et al. 2008; Harper et al, 2008).

Ethical Issues

The ethics of PGD centres on arguments over the moral status of the embryo. Those who believe that being an embryo is as much a part of the lifecycle of a human as an

infant, child or adult, and that life starts when sperm meets egg at fertilisation, tend to find both PGD – where affected embryos are destroyed prior to pregnancy - and Prenatal Diagnosis – where affected fetuses are terminated during pregnancy – unacceptable. However, many feel that there is a moral distinction to be made between the embryo, a small collection of dividing cells; a fetus at 12 weeks of age,when the body shape and major organ systems have formed; and a viable fetus at around 5 months of age – one which could potentially survive birth.

During IVF treatment - a technique which is generally deemed as acceptable and has to date resulted in the birth of more than three million babies worldwide - only the healthiest looking embryos, which are dividing normally and are the right size and shape, are chosen for implantation into the womb. Some people argue that PGD – where embryos are similarly selected based on genetic make up - is no different. Below we will explore some of the applications of PGD which have caused the most controversy in recent years, in some cases challenging the way this technology is regulated.

Social Sex Selection

Before scientists had developed a method for carrying out individual genetic tests on embryos, they first discovered how to identify the sex of the embryo, allowing female embryos to be selected for couples at risk of passing on so-called 'X-linked' disorders – those which are caused by a faulty gene on the X-chromosome and which usually only affect boys.

Most people do not take issue with using sex selection for medical reasons. But where PGD is used to select the sex of a child for social reasons – either personal preference or so-called 'family balancing', where parents wish to have both male and female children – many people find this unacceptable.

For a number of reasons social sex selection is currently banned under UK law. One is that, if the demand were significantly high and biased in either direction, it could cause an imbalance in the sex ratio such as that seen in India and China. Another is that some people regard it as sexist, making the child prone to pressure from parents to adhere to sexual stereotypes.

Nonetheless, there are some who argue that such measures are unnecessary in the UK's current social climate, where boys and girls are by and large favoured equally, and that they compromise people's right to make reproductive choices. Other arguments in favour of the deregulation of sex selection include the fact that PGD is an invasive, costly and extended process for all involved, making it unlikely that many people will choose to undergo the procedure for 'trivial' reasons. Another reason is that some people fear that preventing sex selection via PGD may encourage people to terminate their pregnancy upon discovering that the child is not of the preferred sex. Finally some believe that those who wish to select the sex of their child for the purpose of family balancing are not being 'sexist', but rather wish to have the experience of raising children of opposite sexes.

BOX3: The Mastertons

In 2000, Alan and Louise Masterton, applied to the HFEA for permission to use PGD to conceive a baby girl, following the death of their only daughter in a bonfire accident. Mrs Masterton was sterilised after the birth of her daughter Nicole, who was three years old when she died in 1999. The couple wanted to use IVF to try for a baby girl, by removing Mrs Masterton's eggs and fertilising them with laser-sorted sperm from Mr Masterton. Laser-sorting can separate sperm carrying male Y-chromosomes from those carrying an X-chromosome, but the procedure is not 100 per cent effective. So the couple also wanted to use PGD, to ensure that only female embryos were put back into Mrs Masteron' s womb. The couple, who have four boys aged between 15 and 20 years, said they were not trying to replace their daughter, but wanted the chance to try for another girl.

Their request was turned down and so the Mastertons travelled to a clinic in Italy for the treatment (where PGD was at that time allowed), paying £30,000. After three unsuccessful attempts, the Masterton's decided that the stresses of going through repeat failed IVF cycles were too great, and abandoned the plan.

Late-onset and 'lower penetrance' disorders

Most of the conditions which are licensed for PGD in the UK are serious or untreatable genetic conditions which manifest from birth or early childhood.

However 'late-onset disorders' - those which manifest in adulthood, e.g. Huntington disease or hereditary forms of Alzheimer's, and 'lower penetrance' disorders such as hereditary breast cancer, in which carrying the gene mutation does always not result in the person developing the disease– have now been granted licences in a small number of cases.

Some critics view this as a as a 'slippery slope', worrying that giving permission to test for so-called 'high penetrance' genes - those guaranteed to result in the condition later in adulthood - would make it increasingly difficult to resist requests for ever more trivial reasons, such as lower penetrance genes which confer only a slightly increased risk of developing a condition, with no guarantee that it will ever develop.

Opponents of PGD argue that testing for such conditions would be 'unethical', since children born with such conditions may lead long and fulfilling lives without ever developing the disease. Others point out that those who did develop the disease would be likely to do so after many decades of healthy life and that breast cancer, for example, is now highly treatable with around 8 out of 10 surviving beyond five years after diagnosis.

But not only will a child born into an affected family witness other family members become ill and perhaps die from the disease, they too will spend most of their life knowing of the very real possibility that this will become their own destiny. In families affected by hereditary breast cancer, for example, many women who find out that they are carriers of the gene mutation resort to having their breasts surgically removed – a procedure known as 'prophylactic mastectomy' – before they reach the age when other family members succumbed to the disease. The fact that women in this situation are willing to take such extreme measures to reduce their risk is evidence of the psychological burden they must carry. For them, it must be inconceivable that the desire to avoid the disease can be regarded as trivial.

In the case of Huntington disease, and other non-treatable fatal conditions, some people feel that it is unethical for the parents to have children at all when they are likely to become sick or even die at a time when the child is still dependent on them. Still, in many such cases there is another parent or guardian who would be willing and

able to care for the child in the event that a parent was lost, thus making the situation acceptable for most.

BOX4: Matthew and Helen

In 2007 a London couple – Matthew, 24 and Helen, 25 – applied for permission from the Human Fertility and Embryology Authority (HFEA) – the government's fertility watchdog – to screen their embryos for inherited breast cancer genes. Given their long family history of the disease, the couple wished to use PGD to screen their embryos for faults in a gene – BRCA1 - which raises lifetime risk of a breast cancer to 80%. In a controversial move, the HFEA granted them permission making them the first couple allowed to screen for a genetic condition that merely increases risk of a disease, with no guarantee that the condition will ever develop.

'Saviour Siblings'

Concerns over saviour siblings – children conceived to provide tissue-matched blood stem cell transplants for a sick sibling - revolve around the idea that couples might wish to have a child as a 'means to an end', rather than in its own right. Some argue that this raises concerns over the welfare of the child, who may perhaps not feel as valued as they would if they were conceived under normal circumstances and may even be put under unreasonable pressure to 'save the life' of their sick sibling.

For example, a limitation of this procedure is that only a small number of stem cells can be harvested from the umbilical cord – enough to treat only a small child. In the event that there are not enough stem cells to transplant, the parents may be faced with the difficult decision of whether to, when the sibling is old enough, subject them to a painful bone marrow extraction in order to save the life of the sick sibling, or whether to abandon the quest completely in favour of preserving the younger sibling's autonomy.

Others argue that further research is needed to assess the psychological impact of growing up as a 'saviour sibling'. What if the tissue transplant doesn't work, and the ill sibling dies despite receiving matched blood stem cells – will the donor child, having failed to live up to its parent's expectations, grow up in the shadow of failure?

Many argue that this is unlikely to be the case on the grounds that the resulting effect on the surviving child and its family is unlikely to be so harmful that it would have been better for the saviour sibling not to have been born at all.

Another argument in favour of saviour siblings is that provided a child is loved and valued, it is of no consequence that it is also a source of donor tissue. Furthermore people have children for a variety of reasons – to provide companionship for another child, to inherit a family business or to prop up an ailing marriage – none of which preclude the parents from loving and caring for their offspring.

Currently, whether or not prospective parents should be allowed to select embryos on the basis of tissue type is decided on a case-by-case basis by the Human Fertilisation and Embryology Authority (HFEA) – the government's fertility watchdog. Although some people argue that the conditions under which 'saviour siblings' are allowed should be written down in law, others feel that this would prove too inflexible considering the potential for unforeseen uses of PGD to emerge in future years.

BOX5: The Whitakers

In August 2002, British couple Jason and Michelle Whitaker were refused permission by the HFEA to conceive a child who would be able to provide compatible cord blood for their son Charlie, a decision criticised by many doctors and commentators.

Six-year-old Charlie had Diamond Blackfan anaemia (DBA), a rare blood disorder which meant he had to undergo a blood transfusing every three weeks. Some cases of DBA are caused by a mutation in a known gene, but for most, including Charlie Whitaker, the gene or trigger responsible remains unknown. The family subsequently travelled to have the procedure carried out at a private US fertility clinic in October 2002.

The treatment was successful, and James Whitaker, a potential matched cord blood donor for his sick brother, was born in June 2003. Just over a year later, Charlie underwent a successful bone marrow transplant operation using the cord stem cells

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in October 2004, and was pronounced 'effectively cured' by his doctors in August 2005.

'Designer Babies'

To date, PGD has only been used by couples in relation to a serious genetic disorder in their children. Nonetheless many experts still worry that if genes that influence human traits such as intelligence or sporting ability are discovered it seems possible that some couples might want to select for these too. But is this realistic?

Scientists argue that it isn't. These kinds of traits result from complex interactions between many genes plus environmental factors, they argue, and even if we could identify them all, the chances of having sufficient embryos to select from to realise the desire for intelligent, musical or athletic offspring is almost zero. Furthermore, even if this miraculous feat could be achieved in the future - would anyone want it? Given the limited availability, expense and low success rate of PGD, along with the lengthy and invasive nature of the treatment, it is usually only pursued by those who feel they have no other alternative. In any case, in the UK (and most other countries where PGD is permitted) it is illegal to test embryos for any reason other than to avoid a serious medical condition.

Choosing disability

Many people, perhaps the majority, in today's society view deafness as a disability. Implicitly this would make selecting embryos for traits such as deafness or conditions of short stature an abuse of medical technology and not in the best interests of the child. Nevertheless many people affected by such conditions see them more as a cultural identity than a 'disability' *per se* and in some instances would prefer to have a child who, like them, is affected and can thus share in their unique culture.

The Human Fertilisation and Embryology Bill, which will become law in summer 2008, states that embryos with a 'serious abnormality' should not be preferred to those without such an abnormality. If made law, this would effectively mean that those affected by deafness or dwarfism, and others judged to have a 'serious abnormality', would be forbidden from using PGD or selecting donors to deliberately create a 'disabled' child.

Given that others are entitled to use PGD to choose children 'like them', sharing the same characteristics, language and culture, some people feel that to outlaw this for certain groups of people – those with 'disabilities' - would be an act of discrimination or even of 'eugenics' – controlling who is born. Some ethicists agree with this argument, believing that banning certain people from selecting children from their own unaltered genetic material, while allowing others to do so, is a violation of their reproductive liberty.

Others have questioned the need to legislate PGD at all, believing instead that reproductive decisions are best left in the hands of the prospective parents and their doctors. With the cost and physical and mental stresses of undergoing PGD, scientists and policy makers have argued that such treatments are unlikely to be in high demand, other than for the avoidance of the most serious of genetic disorders. Even so, it is extremely difficult to know where to draw the line.

BOX6: Sharon and Candy

In 2002 an American lesbian couple became parents of the world's first 'designer deaf children'. Sharon Duchesneau and Candy McCullogh, a couple who are deaf themselves, have two children who are both deaf 'by choice' - their mothers privately sought out a deaf sperm donor after fertility clinics refused to do so. At the time the women defended their decision, saying that they would not have rejected a hearing child, just that they hoped for children that were deaf as they would be able to share the same cultural identity as their parents. Their decision, they said, is no different to choosing the colour or gender of a child.

Sharon and Candy hoped that their baby would be deaf - they gambled with nature and won. But the prospect of screening embryos for inherited characteristics using PGD means that some parents now have the option of *choosing* a deaf child, provided that a gene for deafness exists within their gene pool.

Looking Forward

There have been enormous advances in reproductive technology in past decades, leading to the birth of thousands of healthy children and bestowing many with an

experience of parenthood which they perhaps never otherwise could have had. Though many families have now benefitted from the ability to choose embryos unaffected by certain genetic conditions – the main premise of PGD – or as a tissue match for a sick sibling, the awesome power of this technology has not gone unnoticed.

In response to the new ethical and social issues raised by PGD, have emerged equally elaborate regulatory and legal systems. Until recently, it has been the role of the Human Fertility and Embryology Authority (HFEA) to watch over how embryos are used in the doctor's surgery and in the laboratory, guided by their very own Code of Practice. But soon a new Bill in parliament will turn much of the HFEA's Code into law, a move which some critics worry could lack the flexibility necessary to accommodate future technologies.

Given its financial and psychological burdens, coupled with its technical difficulty and relatively low pregnancy rate (compared to natural conception), it seems likely that PGD will remain a specialist medical procedure, attractive only to a minority of people who feel they have no other option. With this is mind, many feel that there are good reasons to resist the temptation to try and define too precisely in law what PGD can or cannot be permitted for. They believe these intensely personal decisions need to be handled on a case-by-case basis and under the supervision of an authority with the experience and expertise to understand all the issues.

Whatever the future holds for PGD, perhaps the real risk lies in missing out on the genuine benefits to be gained from this technology over fears about its potential harms.

Appendix

Chromosomes, Genes and DNA

To understand how healthy embryos are selected from among those with specific genetic defects, it is helpful to understand a bit about the role that genes play inside our bodies.

Like all other multicellular creatures, every human being starts its life as a single cell. As the pregnancy progresses, that cell divides into two and then into four, eight and so on until an entire human is created. With the great complexity of the human body, its vast array of tissues and functions, it may be hard to believe that this miraculous process of embryological development can so frequently result in a healthy bouncing baby - but time after time it does.

The instructions which guide this process are possessed by almost every living cell in the body. They come in the form of genes - sections of DNA which encode instructions for the manufacture of individual proteins by the cell. Despite being smaller than a full stop, every newly fertilised egg contains a complete set of genes – around 25,000 in total - known collectively as the human genome and conveniently packaged into 46 tiny structures called chromosomes (see fig.4).

Each cell is like a specialised factory, producing the exact set of proteins it needs to function. The cell 'reads' the DNA instructions to make these proteins by using a chemical intermediary called RNA. Those genes which are not appropriate in any one cell are inactivated, but are still stored in the cell from the past or for future reference. This means that a change in the genetic code of any one gene (called a mutation) is possessed by every cell in the body right from the moment of conception – an important quality if an embryo is to be used to indicate the genetic makeup of the resulting child.

DNA – and therefore any gene – is made up of two strings of building blocks called nucleotides, coiled together in a double helix shape. There are just four varieties of nucleotides – adenine (A), thymine (T), cytosine (C) and guanine (G). It is the sequence of nucleotides of the gene (AAGTGGCTTT etc,) that contain the 'instructions' for the manufacture of the particular protein that the gene encodes. The nucleotides of the opposing strands of the DNA double helix follow a pairing rule – 'A' always pairs with 'T' and 'C' with 'G'. This means that when the two strands of the DNA double helix separate during cell division, a correct second complementary strand can be constructed alongside each single strand by following the pairing rule - a process called 'DNA replication'.

But the DNA replication process isn't perfect and despite the body's elaborate proof-reading system designed to spot mistakes, errors do occur. Although such gene changes can be harmful, neutral or even beneficial, the term 'mutation' is often used in the context of harmful ones – those which result in a genetic disorder. So when scientists carry out a genetic test on an embryo, they are looking for changes, or errors, in the DNA sequence of a gene which might in turn affect one or more of the proteins made in the body, to alter the way a person grows or develops.

There are over 6,000 known genetic disorders which are caused by a change in a single gene. Knowing the gene which is responsible for a specific condition is important in PGD because the human genome is vast and so, to carry out a genetic test, scientists need to know where to start looking for a gene change. Without this information it would be like searching a library for a book without knowing its title or author.

As well as knowing which gene to look for a mutation in, scientists carrying out PGD need to know the specific gene change, or mutation, that is present in that particular family. This is often a change in a single letter of the DNA code, but can also be a deleted or inserted letter or letters, or some rearrangement of the sequence of the code. Normally, the specific mutation can be identified by carrying out a genetic test on an affected member of the family. However, those families in which a specific mutation cannot be identified, perhaps because the affected member is deceased or is unwilling or unable to consent to a genetic test, are unsuitable for PGD.

Fig. 4: The relationship of a chromosome and DNA to proteins and cells
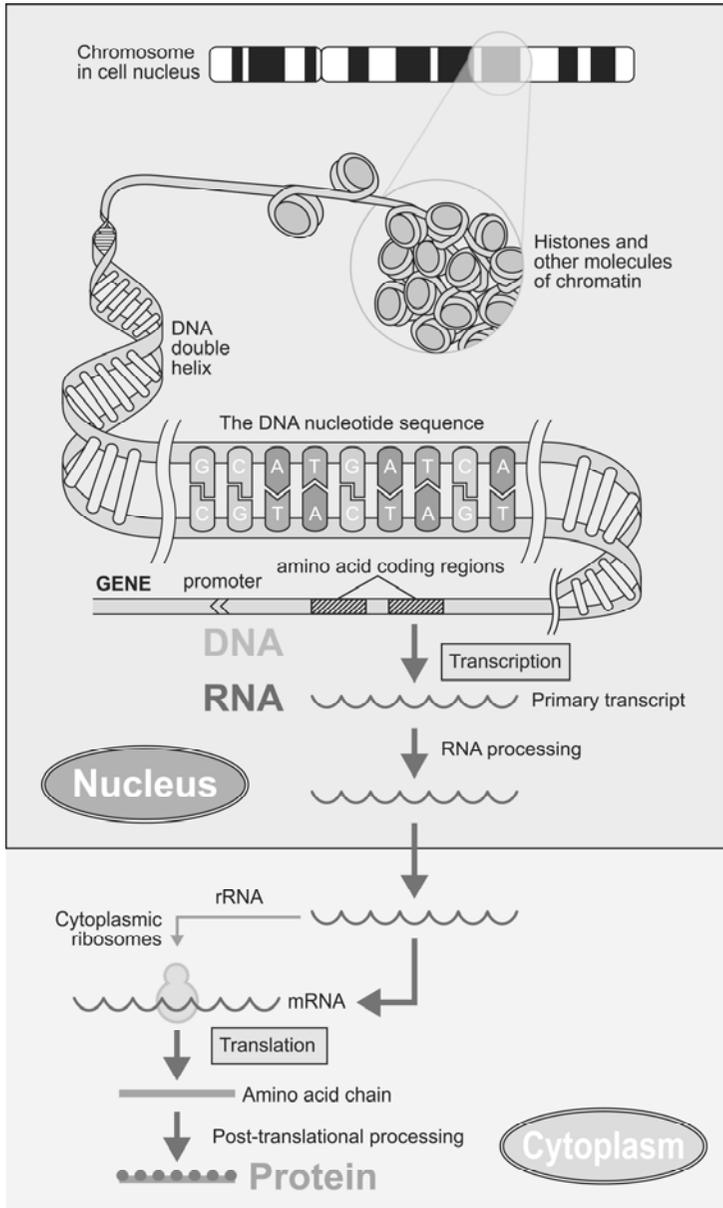
Genes and Inheritance

Because scientists now know how the chromosomes behave during egg and sperm formation, it is possible to explain how certain mutations are passed down through the generations of a family by noting which family members are affected. There are three simple patterns of inheritance. One of these - referred to as X-linked inheritance - relates to gene changes which occur on the X-chromosome and generally affect only boys (XY), as females have two chromosomes (XX) and thus have a working copy which can compensate for the faulty one.

The other two – referred to as autosomal dominant and autosomal recessive inheritance - relate to gene changes within the remaining 22 pairs of chromosomes – known as the 'autosomes' – and uniformly affect both males and females.

Dominant Inheritance

Huntington's disease, polycystic kidney disease, achondroplasia or dwarfism, and neurofibromatosis are all examples of conditions that follow an autosomal dominant pattern of inheritance. In such conditions the effects of the faulty gene are not masked by the working copy and thus if one of the two parents is affected, every child has a one-in-two chance of also being affected.

Recessive Inheritance

Cystic Fibrosis, sickle cell disease and Tay-Sachs disease are all examples of conditions that follow an autosomal recessive pattern of inheritance and in fact most genetic conditions follow this pattern. In such conditions the effects of the faulty gene may be masked by a working copy, so only those who inherit a faulty copy from both parents are affected.

X-linked Inheritance

Duchenne muscular dystrophy, haemophilia and Fragile X syndrome are all examples of genetic conditions that follow an X-linked recessive inheritance pattern of inheritance. In such conditions the effects of the faulty gene usually only affect boys as they are born with only one X-chromosome and thus do not have a working copy

to compensate for the faulty one. This means that any son born to a female carrier has a one-in-two chance of being affected, while each of her daughters has a one-in-two chance of being carriers themselves.

Further Reading

BOOK: Sarah Franklin and Celia Roberts. *Born and Made: An Ethnography of Preimplantation Genetic Diagnosis*. Princeton University Press (2006).
An innovative analysis of preimplantation genetic diagnosis through an ethnographic account of scientists, clinicians, genetic counsellors and patients.

BOOK: Jonathan Glover. *Choosing Children: Genes, Disability, and Design.* Oxford University Press (2006).
This beautifully clear book is written for anyone who cares about the rights and wrongs of parents' choices for their children.

BOOK: Jess Buxton and Jon Turney. *The Rough Guide to Genes and Cloning.* Rough Guides Reference Titles (2007).
This clearly written book provides an excellent introduction to genetics, considering everything from Dolly the sheep to designer babies.

BOOK: *A Guide to Genetics,* Progress Educational Trust (2006)
This concise book (third edition) covers basic processes in human genetics, genetic testing, gene therapy and embryo testing, as well as ethical issues raised by genetic technologies. Available from the UK charity Progress Educational Trust for £6.49 (www.progress.org.uk) telephone 020 7278 7870.

BOOK: Robert Winston. *A child against all odds.* Transworld Publishers (2006).
A definitive account and a personal view of modern reproductive technology and the ethical problems that it raises, written by a scientist at the forefront of this field.

WEBSITE: BioNews
http://www.bionews.org.uk

BioNews is a free web and email-based source of news, information and comment in human genetics and assisted reproduction, produced by the UK charity Progress Educational Trust.

WEBSITE: Human Fertility and Embryology Authority
http://www.hfea.gov.uk
The Human Fertilisation and Embryology Authority is the UK's independent regulator overseeing safe and appropriate practice in fertility treatment and embryo research. Search their website for clinics carrying out PGD and up-to-date information about genetic conditions currently licensed for PGD.

WEBSITE: European Society of Human Reproduction and Embryology (ESHRE)
http://www.eshre.com
A society dedicated to study and research in the field of reproductive medicine and science.

Glossary

Aneuploidy   A condition in which there is an abnormal number of chromosomes, either fewer or more than is usual (46 in a human body cell).

Autosomal dominant inheritance A pattern of inheritance in which a gene change has an effect even if only one copy is inherited, e.g. the mutated gene that causes Huntington's disease. Also known simply as dominant inheritance.

Autosomal recessive inheritance   A pattern of inheritance in which a gene change has an effect only if two copies are inherited – the mutated gene that causes cystic fibrosis, for instance. Also known simply as recessive inheritance.

Autosome   Any human chromosome apart from the sex chromosomes, X and Y. There are 22 pairs of autosomes, numbered 1-22.

Beckwith Wiedemann syndrome (BWS) is a rare genetic or epigenetic disorder (prevalence of about 1 in 15,000) that causes large body size, large organs, and other problems. BWS is triggered by mutations in growth regulating genes on chromosome 11, caused by an inversion specifically on 11p15, or by errors in genomic imprinting.

Carrier   An individual who has a disease-causing gene mutation on one chromosome of a pair, and a normal version on the other. Usually refers to unaffected carriers of recessive conditions.

Chromosome   Chromosomes are tightly packaged bundles of DNA, the chemical that encodes genetic information. Nearly all human body cells have a set of 46 chromosomes, while eggs and sperm have 23.

DNA   Deoxyribonucleic Acid is the chemical that encodes genetic information. It contains four different chemicals, or bases, known as A (adenine), C (cytosine), G (guanine) and T (thymine).

Embryo   A stage of development (before fetus stage) during which tissues and organs are formed. In humans this stage lasts for eight weeks after the fertilised egg first starts to divide.

Fetus   A stage of development (after the embryo stage) when all organs have been formed. In humans, this stage lasts from nine weeks after fertilisation until birth.

Fluorescent in situ hybridisation (FISH)   A lab technique that uses fluorescently-labelled pieces of DNA to detect specific genes, chromosome segments or chromosomes in cells examined under a special microscope.

Gene   The basic biological unit of inheritance. Genes are made out of DNA, and most are coded instructions for making proteins. Others make molecules that control gene activity.

Genetic condition   A condition or illness caused by changes in a gene or genes, affecting the way the body looks, develops or works.

Genetic counselling   Information and advice given to patients affected by, or at risk of a genetic condition. An explanation of risks and options may include the findings of specific gene tests.

Genetic susceptibility/predisposition Increased probability (compared to the general population) of developing a disease due to the presence of one or more genetic mutations.

Genetic Test A test that gives genetic information, for example about disease status or susceptibility.

Genome The total genetic information of a living thing, a complete copy of which is found in most body cells. The human genome is made up of around 2.9 billion chemical letters (base-pairs) of DNA.

Intracytoplasmic sperm injection (ICSI) A treatment developed to treat male infertility, which involves injecting a single sperm into an egg. Also used in PGD for single-gene disorders to avoid contamination of the PCR sample with non-embryonic DNA from surplus sperm.

Imprinting The process by which certain mammalian genes are "switched off", depending to whether they were inherited from father or mother.

In vitro fertilisation (IVF) A treatment for infertility in which eggs are removed from a woman's body, fertilised with sperm in a laboratory, then returned to the womb shortly afterwards to continue developing.

Mosaicism The occurrence of two or more cell populations within a single tissue or individual, which have different genetic constitutions.

Mutation A change in the genetic information of an individual, which may have a harmful, neutral or beneficial affect.

Penetrance The extent to which a mutation causing a particular disorder causes clinical symptoms of that disorder. Usually refers to autosomal dominant conditions.

Polymerase Chain Reaction (PCR) A laboratory technique used to make millions of copies of a known piece of DNA, used in many medical and forensic tests.

Pre-implantation Genetic Diagnosis (PGD) PGD is a genetic test that can be carried out on embryos created using *in vitro* fertilisation (IVF) to ensure that only embryos unaffected by a particular genetic condition are returned to the woman's womb.

Prenatal Diagnosis   Biochemical, genetic or ultrasound test preformed during pregnancy to determine if a fetus is affected by a particular disorder.

Sex chromosomes   Refers to the two chromosomes (X and Y) that determine the sex of an individual.

Single Gene Disorder   A disorder caused by a mutation in a single gene. Cystic fibrosis, for example, is caused by a mutation in the CFTR gene.

Stem Cell   A type of unspecialised cell which is capable of developing into all (multipotent) or a wide range of (pluripotent) different body tissues. May be derived from early embryos, umbilical cord blood and certain body tissues such as bone marrow.

X-linked inheritance   A pattern of inheritance caused by a gene mutation located on the X-chromosome. Usually recessive – affects only boys (XY) but females (XX) can be carriers.

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A Guide to Pre-implantation Genetic Diagnosis

Since 1989 it has been possible to create embryos, by mixing sperm and eggs in the laboratory, and then to test them for certain genetic and chromosomal conditions, using a technique called Pre-implantation Genetic Diagnosis (PGD). When PGD first became available, it was used primarily by couples known to be at high risk of passing on a serious genetic disorder to their children. But in more recent years a number of unforeseen uses of PGD have emerged, making headlines and attracting a firestorm of responses from both scientists and the public.

This guide aims to highlight the relevant procedures and technologies behind PGD, as well as its past, present and future applications. By shedding light on some of the important ethical and legal dilemmas raised by this technology, this booklet provides information for those who may wish to join the debate over PGD, who need to make use of PGD themselves, or who just want to learn more about the subject.

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