Building healthy families

New developments in genetic diagnosis have given birth to a number of ethical dilemmas

When *in vitro* fertilization (IVF) was first used 25 years ago to 'conceive' a healthy baby girl, it was met with huge opposition over the ethical and moral implications of this 'unnatural' technology. Since then, IVF has produced an estimated one million babies and the vehement opposition has died down as more babies are born. Now, the use of preimplantation genetic diagnosis (PGD) to screen embryos against inherited diseases has again rallied opponents and moved IVF back into the crosshairs of critics. In particular, the case of Adam Nash grabbed headlines in the USA; Adam was 'created' from an embryo that had been screened using PGD and human leukocyte antigen (HLA) tissue typing. As a result, he is not only free from the Fanconi anaemia that afflicts his sister Molly but is also a perfect genetic match for her. After Adam's birth, stem cells taken from the umbilical cord were used to treat Molly's disease. More recently, after a prolonged legal battle with UK authorities, the Hashmi family finally received permission in April this year to use PGD and tissue typing to select an embryo in the hope of having a healthy baby to treat their son Zain, who suffers from β -thalassaemia. These and other cases have received significant publicity and have prompted heated debates over the ethics of using PGD to select for specific traits.

For couples haunted by a family history of genetic disease, there are few reproductive choices. Aside from adopting a child or using IVF with donated eggs or sperm, they can either take the risk of conceiving a child with the disease, or not have children at all. PGD has changed this, and it is now possible to have a child without passing down an inherited disease. Mark Hughes, now a professor at the Center of Molecular Medicine and Genetics at Wayne State University School of Medicine (Detroit, MI, USA), first

developed PGD in the mid-1980s while at Baylor College of Medicine (Houston, TX, USA), and with British colleagues Robert Winston and Alan Handyside used it to screen embryos for cystic fibrosis (CF). The technology was soon extended to many other heritable diseases (see sidebar). PGD is performed on an embryo created through IVF that has developed to the 6–8-cell stage.

SOME DISEASES THAT CAN BE TESTED FOR BY PGD

Achondroplasia
Adenosine deaminase deficiency
Alzheimer's disease
 β -Thalassaemia
Cystic fibrosis
Down's syndrome
Duchenne muscular dystrophy (DMD)
Fanconi anaemia
Fragile X syndrome
Gaucher disease
Haemophilia A and B
Hunter's syndrome
Huntington's disease
Hypophosphataemia
Incontinentia pigmenti
Lesch–Nyhan syndrome
Marfan syndrome
Myotonic dystrophy
Neurofibromatosis type 1
OTC deficiency
Phenylketonuria
Polyposis coli
Pseudohyperparathyroidism
Retinitis pigmentosa
Retinoblastoma
Rett's syndrome
Sensory motor neuron diseases
Severe combined immunodeficiency syndrome (SCIDS)
Sickle-cell anaemia
Spinal muscular atrophy (SMA)
Tay–Sachs disease
Vitamin D-resistant rickets

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Using micro-manipulation techniques, one of those cells is removed for testing either by PCR, to screen for mutated genes, or fluorescence *in situ* hybridization, to detect chromosomal aberrations. Healthy embryos are then transplanted to the uterus. Using PGD to select only 'healthy' embryos removes the need for repeated terminations—before its advent, couples with a family history of severe disease had to rely on invasive prenatal diagnoses and had to make the difficult choice of whether to abort if the fetus was found to carry the disease in question.

Even though it has this potential, "PGD raises very different questions" from IVF, Arthur Caplan, Professor of Bioethics at the University of Pennsylvania (Philadelphia, PA, USA), said. Whereas IVF raised issues of safety and unnaturalness, "PGD raises questions of what constitutes a disease, when should doctors honor parental requests to screen embryos, can an embryo be destroyed for a non-life threatening condition and what levels of accuracy should be expected when couples use PGD and spend a lot of money to do so." Unlike the fears associated with IVF, none of these difficult questions will disappear with the birth of a healthy baby.

Although PGD can theoretically be used to screen for any disease for which the genetic mutation is known, Hughes emphasized that embryos are not tested for every potential disease—only those have already been identified as being a risk. "You don't do tests to go hunting. That would be like saying, 'let's put up a CAT scanner or an MRI scanner out on the street and everyone that's walking along; let's run them

through and see what we might find'. He stressed that PGD is designed solely for families who are already at risk of passing down a serious disease to their offspring. Gregory Stock, Director of the Program on Medicine, Technology and Society at the University of California at Los Angeles (CA, USA) echoed these sentiments, saying, "It's really not very useful except for people that are at high risk of particular genetic disorders."

Despite the obvious benefit in eradicating devastating diseases from individual families, an ethical and moral debate was ignited when couples and their doctors went one step further and combined PGD with HLA typing to select an embryo whose birth could benefit an ill sibling. With each publicized case, even more issues come to the fore. In June, British couple Michelle and Jayson Whitaker had baby Jamie, who had been selected to cure his brother Charlie's Diamond-Blackfan anaemia. The Whitakers undertook their treatment in the USA after British authorities refused to give them permission on technical grounds. This case has highlighted the fear that, when the use of such technology is restricted, couples will go elsewhere for treatment. By banning PGD, Stock

thinks, "it simply reserves the technology for those who are affluent and educated" because they will simply travel to another country where the technology is allowed. But Thomas Baldwin, head of the Department of Philosophy at the University of York, and deputy chair of the UK Human Fertility and Embryology Authority (HFEA), which regulates IVF and PGD in the UK, disagrees: "The fact that some people will go abroad to receive expensive treatment is not a reason for a regulatory authority to permit that treatment if the authority has concluded that the treatment is inherently risky or unacceptable."

The regulations that govern PGD differ greatly around the world as a reflection of social, cultural and religious beliefs. The US Congress has banned the use of federal funds for embryo research, but the government has no control or influence over the use of IVF and PGD in private institutions. Controversy instead arises over the issue of 'playing God', and the similarities between discarding unused embryos and aborting fetuses. As Hughes admitted, "In America, probably nothing since the Civil War has divided our nation quite like ... this

whole issue of abortion." With no governmental legislation, ultimately clinics are free to offer PGD and use it for any reason they see fit according to their definition of what constitutes an ethical use of the technology. Baldwin believes that "It is essentially a political matter there, reflecting the curious political culture of the place. It is certainly not a good model for the rest of the world."

In the UK, IVF clinics and the use of PGD are regulated by the HFEA under the rules defined by the Human Fertilization and Embryology Act. In the rest of Europe, attitudes vary, with some countries allowing PGD for screening against severe, non-treatable diseases. Germany takes the opposite stance. Any diagnostic technique on an embryo before the 8-cell stage is at present prohibited by the Embryo Protection Act and is punishable by imprisonment. This year, the German National Ethics Council, recommended that the prohibition of PGD should continue, although 15 of the 24 council members supported its use for strictly limited medical reasons. Edgar Dahl, an ethicist at the Center for Dermatology and Andrology at the University of Giessen, Germany, admitted, "I really think that Germans are generally overly cautious when it comes to the application of new reproductive technologies or human genetics." Understandably, Germans have more at stake when contemplating any technology that might be construed as advocating selection, because it resurrects the ghosts of the Nazi atrocities committed in the name of eugenics.

Because chromosomal content is easily assessed when screening embryos against disease, there are additional ethical reservations that this could be used to select embryos for gender. Apart from avoiding the inheritance of a sex-linked disorder, parents might want to 'balance' the sex ratio in their family or have more control over the birth order of their children. Surveys showed that, in the West at least, giving parents this option would not skew the sex distribution too much. Dahl recently published the results of two surveys about Germans' and Britons' attitudes to sex selection (Dahl *et al.*, *Human Reproduction*, **18**, 2231–2234, 2238–2239; 2003). He and his colleagues found that, although the UK and Germany differed in other attitudes, there was no significant preference for boys or girls. Similar surveys in the USA have also suggested that no marked change in sex distribution would

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occur if parents were allowed to choose the sex of their children. An absence of bias is not the only reason: "PGD is so inconvenient and so expensive that it will have no impact on the overall distribution of sex ratios anywhere in the world. It is not a practical technique for large-scale sex selection," Caplan said. However, other countries, where cultural and social traditions dictate that sons are more valuable than daughters, might not be so unbiased. The possibility of sex selection has therefore raised the question of whether it is hypocritical to advocate it in the West, while condemning countries such as India and China for essentially doing the same thing, although by more drastic means. "To me, those are larger social issues that are not best dealt with by trying to regulate the technology itself," Stock said. Dahl agrees that this question must be left to each country to deal with: "We cannot punish the people of our countries for the crimes committed in another country." Baldwin said, "the issue of what kind of example we set in the area of sex selection is an important one, though, equally, we in the 'west' should not arrogantly assume that our policies are right for everyone. There is a delicate balance to be struck in this area."

There are fears that PGD will eventually be used to select for non-medical traits such as intelligence, appearance and physical prowess, which concerns both advocates and opponents. Referring to his surveys in the UK and Germany, Dahl noted that this should not be overestimated. Of the small proportion of people who would use sex selection, an even smaller subset would use genetic diagnosis techniques to select for other traits. "I think the reference to the slippery slope presupposes something that's simply not right," he said. Hughes also believes that widespread selection of non-medical traits is unlikely, but for different reasons. "No one in their right mind would go through IVF technology if they didn't have to. You're not going to do this for a trivial reason." But even if the practice does not become widespread, Stock admitted, "I think that as we move forward in this realm, it is a certainty that everybody's sensitivities are going to be stepped upon by someone." He stressed, however, that a few

troublesome cases do not necessarily warrant strict regulations. Hughes agreed, "You can have a Domsday kind of attitude about it or you can say let's move forward in a responsible careful way, and evaluate and make sure that it's used properly."

Because PGD is a new technology in reproductive medicine, there are additional concerns about its safety and about its legal and commercial implications. PGD results are tracked in the UK, but private clinics in the USA are under no obligation to record their successes and failures. Across Europe, the European Society of Human Reproduction and Embryology (ESHRE) has created a PGD consortium to monitor its use and to produce guidelines and recommendations. But participation in the ESHRE's assessment is purely voluntary. In the meantime, mistakes in PGD have been publicized, with at least one fetus being found to contain the mutated gene that it was originally selected against; in a litigious country like the USA, the legal repercussions could be extensive. "I think you will move towards various kinds of wrongful birth suits and things of that sort," Stock said, but cautioned that such lawsuits will be as likely outside the USA as within. Caplan worries more about what social and economic pressures will do to the future of PGD and the

selection of non-medical traits. "Those pressures combined with aggressive marketing and advertising are what I worry about the most with respect to future genetic testing of gametes and embryos," he admitted.

"It's helping couples build healthy families, and what could be better than that?"

Given the difficulties involved in IVF, PGD will probably never become a standard service for prospective parents but will be reserved for individual cases in the most need. Hughes even hopes that one day it will be obsolete. As he pointed out, 11 years ago when PGD was first used, children with CF never had to worry about passing down the gene—they did not live long enough to have children. But now, modern pharmaceuticals and medical treatments mean that those suffering from CF live much longer. "Today's devastating diseases are hopefully tomorrow's cures and that's where we need to be focused," he said. In the meantime, "it's helping couples build healthy families, and what could be better than that?"

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doi:10.1038/sj.embor.7400023

Pioneers in medicine

Small countries are taking big steps towards improved genetics-based research and health care with the creation of population databanks

Sometimes revolutions begin in the most unlikely of places. Iceland is a piece of volcanic rock in the middle of the Atlantic Ocean, inhabited by less than 300,000 people. Estonia is now the easternmost outpost of the European Union, after an overwhelming majority of its people voted on 14 September to join the EU. The country only gained its independence from the former Soviet Union in 1991, and the consequences of Soviet rule are still reverberating. But both countries are leading the way in the next revolution in medicine by establishing DNA and health databases of their populations, something that most larger countries have not yet begun to consider.

"Many people are talking about population genetics, but you in Estonia are doing it," said John Norton, Director and CEO of the UK Biobank Project, at the Gene Forum 2003 conference in Tartu, Estonia, this September. In fact, it seems to be easier for smaller countries, such as Iceland and Estonia, to go ahead with such initiatives. "Establishing a database is of course easier in Estonia with its small population [of 1.4 million people]," agreed Arvo Tikk, chairman of the Ethics Committee of the Estonian Genome Project (EGP) Foundation, not only for logistical reasons but also because it is easier to convince the public, and to adapt the laws and regulations.