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

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 raises 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.

**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
- Frasier syndrome
- Gaucher disease
- Haemophilia A and B
- Hunter’s syndrome
- Huntington’s disease
- Hypophosphataemia
- Incontinentia pigmenti
- Lesch–Nyhan syndrome
- Marfan’s syndrome
- Myotonic dystrophy
- Neurofibromatosis type 1
- OTC deficiency
- Phenylketonuria
- Polyposis coli
- Pseudohyperparathyroidism
- Retinitis pigmentosa
- Retinoblastoma
- Retts syndrome
- Sensory motor neuron diseases
- Severe combined immunodeficiency syndrome (SCIDS)
- Sickle-cell anaemia
- Spinal muscular atrophy (SMA)
- Tay–Sachs disease
- Vitamin D-resistant rickets

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 every-one that’s walking along; let’s run them”
EMBO reports

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technical grounds. This case has highlighted
the fear that, when the use of such technol-
yogy 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 insti-
tutions. 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 govern-
mental 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, atti-
tudes vary, with some countries allowing
PGD for screening against severe, non-
treatable diseases, Germany takes the oppo-
site 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, recom-
pended 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, admit-
ted, "I really think that Germans are generally
overly cautious when it comes to the applica-
tion of new reproductive technologies or
human genetics." Understandably, Germans
have more at stake when contemplating any
technology that might be construed as advoc-
cating selection, because it resurrects the
ghosts of the Nazi atrocities committed in
the name of eugenics.

Because chromosomal content is easi-
ly 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 dis-
order, parents might want to 'balance' the
sex ratio in their family or have more con-
trol 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 recent-
ly 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

through and see what we might find?". He
stressed that PGD is designed solely for fami-
lies 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."
"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."

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 Doomsday 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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**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.