

# Genetic interventions to ‘have healthier children’: a viewpoint from the United Kingdom

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## How far are we prepared to go?

In October 2016, a British actor, Sally Phillips, produced and presented a documentary for the BBC that ignited a furious discussion in the United Kingdom. Entitled *A World Without Down’s Syndrome?* the programme introduced viewers to Phillips’ own son, Ollie, born with Down’s syndrome. It went on to discuss the range of methods now available to detect a foetus with Down’s syndrome, the statistics about the proportion of people who choose to terminate a Down’s pregnancy, and the quality of life of people with Down’s syndrome [1].

Phillips’ documentary was prompted by the announcement that the UK National Screening Committee was about to recommend clinical use of a new, noninvasive method of detecting trisomy 21 prenatally. Unlike amniocentesis or chorionic villus sampling (CVS), noninvasive prenatal testing (NIPT) or diagnosis (NIPD) requires only maternal blood samples, not tissue from the foetus. It is considered a major advance in screening for Down’s (and, in the future, other conditions) because of its relative ease and accuracy [2]. Phillips’ documentary was controversial not because she challenged any of the benefits of NIPT, but because it asked a different question: Do we really want a world without Down’s syndrome? More generally, how far are we prepared to go to ensure we have healthy children?

To many people the answers to both those questions are obvious. They argue that Down’s syndrome constitutes a significant impairment that severely compromises a person’s ability to flourish, and therefore is obviously something we should strive to eradicate from the world, by preventing people being born with it if we can. In this short viewpoint article I want to consider some of the factors that make this question more complex than it appears at first sight. I will focus on the situation in the United Kingdom, because it is often perceived as one of the most permissive countries in the world for research involving human embryos or innovative therapies to treat infertility or identify genetic conditions. In some senses this is true, in that the law allows forms of research or treatment that other European countries do not. At the same time, however, the UK’s practices are highly constrained by law and through the activities of the national regulator, the Human Fertilisation and Embryology Authority (HFEA), which (for example) has the authority to decide whether

or not clinics can be licensed to offer certain kinds of fertility treatment. Moreover, it is now standard to require forms of public debate or consultation before any significant changes in the law are made or new interventions are offered for clinical use. This happened with mitochondrial replacement technology (MRT) to avoid mitochondrial disease, for example, which saw the publication of several expert reports and a large scale national public consultation, as well as extensive parliamentary debate [3–7]. The Nuffield Council on Bioethics is currently (December 2016) working on a report on the ethics of genome editing in human reproduction, which will probably be published in late 2017; its findings are hard to predict, but it will very likely recommend another national public consultation before any steps are taken to develop gene editing into a feasible method of ‘having healthier children’.

## Prenatal screening, testing and intervention

NIPT is among the constantly growing repertoire of techniques of prenatal identification of anomalies (often but not always genetically influenced) that lead to the impaired health or disability of the future child. These techniques are generally positioned as health interventions: they are provided by a country’s antenatal healthcare services with the promise of helping parents to have healthy (or healthier) children. In the UK, the national Fetal Anomaly Screening Programme (FASP) offers screening for a range of abnormalities that are detectable by ultrasound, as well as chromosomal abnormalities, such as trisomy 21, that need to be confirmed by further amniocentesis or chorionic villus sampling [8]. Note that these are *general population screening* programmes; for those women and couples believed to be at specially heightened risk of a known genetic disorder, targeted prenatal diagnosis may be offered if testing is available for the relevant gene or genes.

Prenatal diagnosis (PND) of foetal anomaly has been with us for a long time, ever since the late 1960s when it was realized that karyotyping of the foetus could detect the extra chromosome 21 that leads to Down’s syndrome. Whether genetic or other, PND is done in order to inform parents (and the health service) that a foetus is likely to have a health condition or an impairment that would generally be considered disabling. The ben-

efit is not to the child, since at the moment relatively few prenatally detected serious anomalies can be treated in any way, but to the parents, who are then faced with two options: to prepare for their future life with a disabled or chronically ill child, or to terminate the pregnancy (in those legislatures which, like the UK, allow abortion for foetal abnormality).

All forms of prenatal screening and diagnosis raise ethical issues, some quite general, others more specific (or apparently specific) to the particular technology, that have been exhaustively rehearsed in the bioethical literature. The most obvious and well-trodden ethical concerns around prenatal identification of anomaly relate to the moral gravity of *abortion*. Morally (as well as legally in some cases), an anomaly must be predicted to have an impact on the child's future life that is severe enough to make the option of termination preferable, at least from the parents' point of view (note that this is not the same as saying that the anomaly must make the future person's life not worth living; many factors other than the subjective quality of life of the disabled individual may legitimately come into the parents' assessment of whether or not to continue with the pregnancy).

With preimplantation genetic diagnosis (PGD), the ethical calculation is subtly but significantly different from that of PND [9, 10]. PGD entails the genetic testing of embryos created outside the body through IVF. Instead of the termination of an otherwise viable foetus, PGD involves not selecting (in practice this usually means discarding) a very early embryo. PGD has been legally available in the UK for a defined list of familial conditions and from licensed clinics since 2009. To many people, the moral gravity of discarding an eight-cell embryo is significantly less than that of terminating a foetus: the developmental stage is seen as morally salient in this case. As a consequence, it may arguably be thought morally permissible to select against more minor anomalies with PGD than would be acceptable for PND. On the other hand, PGD is currently much more technically demanding and figures from the clinics licensed to perform PGD under UK law show that in 2010, the year for which most recent data are available, 131 babies were born from PGD [11] while 2290 terminations were carried out on the grounds of foetal anomaly [12]. This gives a rough sense of the relative uptake of the two methods.

In the future, however, diagnosis and selection as routes to 'having healthy children' will be complemented by more active interventions. For example, the UK has been a primary driver of the development of mitochondrial replacement technologies (MRTs) – and also of the ethical debates about their use. MRTs are intended as therapies for women affected by mitochondrial disease. Mitochondria are subcellular organelles involved in generating cellular energy, maternally transmitted through the cytoplasm of a woman's ovum. Mitochondrial diseases are most commonly due to ab-

normalities of the small amount of autonomous DNA carried by each mitochondrion and present with a diverse array of symptoms and prognoses. It has been estimated that 1 in 400 people in the UK carry a disease-causing mitochondrial mutation, and around 9 in every 100 000 people are clinically affected by mitochondrial disease [13, 14]. The newly developed MRTs involve replacing affected mitochondria by transferring DNA from the nuclei of the intending parents' gametes into an enucleated egg provided by an unaffected donor.

In the UK, the ethical evaluation of MRTs has involved several years of discussion, professional consultations carried out by the Nuffield Council on Bioethics and the HFEA [3–5] and public consultations run by the HFEA and the Department of Health [6, 7]. These debates and consultations were needed not simply to gauge public opinion towards MRTs; the introduction of these methods required the revision of the Human Fertilisation and Embryology Act, last amended in 2008, to enable MRTs to be progressed to therapeutic use by women affected by mitochondrial disease. In December 2016, the HFEA finally approved the use of MRT in treatment, meaning that licensed IVF clinics can now apply to the HFEA if they wish to offer this technique as a means of avoiding mitochondrial disease [15].<sup>1</sup>

More futuristically, the possibility of so-called 'genomic editing' opened up by CRISPR-Cas9 and related technologies has long-term but obvious implications for reproductive choice [16, 17]. It is almost certain that genome editing will first see major practical and commercial use in basic research, in farming (agriculture and animal husbandry), and also in the therapeutic delivery of manipulated somatic cells [18]. However, by far the most public and professional interest, not to say controversy, has been generated by the prospect of using CRISPR-Cas9 to manipulate the human genome, and what that means for the feasibility of transforming the genetic constitution, in a precise and reliable way, of individual humans and also, crucially, their descendants, if genomic editing is not restricted to somatic cells.

## Regulation and legislation

For the UK and other European countries, the reality of genomic editing is a long way off, for regulatory more than technical reasons. British legislation currently forbids any genetic manipulation of embryos (other than the mitochondrial genome in MRT) that would be transferred for pregnancy. Moreover, there is a long-standing and virtually universal consensus against introducing heritable changes into the human germline.

<sup>1</sup> In fact the first reports of the clinical use of MRTs were not related to avoiding mitochondrial disease, but to assisted conception.

Nevertheless, targeted genomic changes have been achieved in model animal systems, and there is no a priori reason to imagine that this will not be possible in humans too; the modification of (non-viable) human embryos has already been reported by China-based research teams [19, 20].

### **But what exactly do we mean by having healthier children?**

The earliest announcements about CRISPR-Cas9 technology and its potential were soon followed by calls from scientists and the media for ethicists to “get involved in the debate”. This unsurprisingly caused a certain degree of irritation among bioethicists, who can point to a decades-long track record of analysing and evaluating the ethics of genetic manipulation, the crafting of regulation that is culturally acceptable and at the same time internationally coherent, how to ensure that access to the interventions that improve health is distributed justly and equitably, and so on. And again, the UK has been at the cutting edge of these discussions.

Nevertheless, I would agree that despite the decades of work there remain some fundamental confusions and under-examined areas which require a different level of exploration, or at least clarifying as far as possible, if we are not to risk pushing thoughtlessly into practices that are fundamentally unjust, dangerous, and unimaginative.

First of all, the claim that improvement of the health of children is the primary goal of cutting-edge genetic (and other) interventions inevitably downplays the most effective way of improving children’s health, everywhere: ensuring universal access to mundane public health measures. There is very little point in grappling with the complex ethics of the permissibility of germline interventions to prevent children inheriting devastating conditions if there are no measles or polio vaccination programmes to keep them alive later on.

Second, there is a persistent and frustrating vagueness about exactly what it is that prenatal genetic interventions provided by healthcare services aim to achieve. If the goal is to have healthy (or healthier) children, then prerequisites for achieving this effectively include both a workable consensus on what a healthy human being is, and reasonable confidence that we know how much a person’s genetic make-up contributes to that end result. The rapid accumulation of genomic knowledge means that we are working towards that confidence for some well-defined conditions, but for the most part still have only a crude understanding of how genomic components interact with each other and with their environments to produce particular states of being. In other words, researchers, ethicists and public health officials alike should be careful to be realistic in the promissory notes they offer to society.

Third, I suggest there is a need for a generally deeper and more critical engagement with the relationship between *health* per se, and an individual’s capacity to have a good and flourishing life – an even more fundamental goal, but possibly one that in contemporary Britain (and elsewhere) seems too abstract and contested to aim for. What *is* a good life? Is it essential to be healthy to have one? Is health desirable, but not essential? Is it necessary, but not sufficient? Is it perhaps, from some perspectives, even irrelevant to human flourishing? And if so, are there cultural and social conditions that might foster the ability to flourish in ways that make health status less important?

Fourth, what is the connection between health (however defined) and the deviations from a phenotypic norm that we refer to as disability? Parents and physicians often speak rather loosely as if prenatal screening means ensuring a healthy baby; but in the main, it is still about identifying foetuses that we believe will experience physical and mental disability, and many disabled people would argue that this has little or nothing to do with health as we normally understand it. A child born with a sensory or mobility impairment, unless that is combined with some other condition or leads to secondary problems, is not ill; s/he faces distinct difficulties and barriers, but overall is likely to be just about as healthy as a child without an impairment. If this is the case, why are prenatal or neonatal screening, testing and (in the future) restorative interventions to alter the mitochondrial or nuclear genome located firmly within the domain of healthcare? Would a different conceptual or disciplinary location be more helpful in thinking through ethical, practical and policy constraints?

And fifth (although probably not finally), there is a need for more thoughtful characterization of the relationship between physical or mental deviations from a phenotypic norm, and what we term disability. I have argued elsewhere [21] that *disability is bad* by virtue of the suffering or disadvantage it introduces into a person’s life, and therefore that it cannot and should not be straightforwardly conflated with phenotypic deviations, many of which are neutral characteristics or have only a trivial impact on the individual’s ability to flourish. The various models of disability that have been developed over the last 40 years argue plausibly that genetically associated variations are not *inherently* disabling; how much disadvantage or suffering they cause may depend more on contingent circumstances (such as the availability of prostheses) than on genes.

Although necessarily informed by science and empirical knowledge, these are issues that lie at the heart of theoretical bioethics. Discussion of them has been foreclosed, largely (I think) because of the availability of health technologies that increasingly gives us the capacity to prevent or select certain genetically influenced conditions. This availability has led to the as-

sumption that society is agreed on what we want to prevent or select for or against. It will be interesting to see how the United Kingdom attempts to balance its orientation towards pragmatic, policy and regulation-focused bioethics with the need to consider these long-standing philosophical concerns, as the options for 'having healthier children' expand over the years to come.

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