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1 Good Parents and New Reproductive Technologies

1.1 Introduction

Humans have always had the ability to influence the genetic makeup of their children. Individuals who wanted tall and attractive children, for instance, could find tall and attractive partners to reproduce with, thereby raising the probability that their progeny would be tall and attractive. However, until very recently, this power was limited. Individuals were often not lucky enough to have a wide range of sexual partners to choose from. Even if they did, there was no guarantee that their children would inherit the traits that were desired.

The past few decades have seen a rapid increase in the power of parents to influence the genetic makeup of their children. Since the 1990s, a range of biotechnology tools have been available, which give parents some degree of control over the genetic makeup of their children. Such technologies are rapidly expanding. In April 2015, it was announced that the gene editing (GE) technique, clustered regularly interspaced short palindromic repeats (CRISPR), had been used to make edits in human embryos for the first time. The study was conducted in China on the disease beta thalassemia – with mixed success (Liang et al. 2015). In February 2016, the UK became the first country to officially approve GE research in human embryos. The decision means experiments in which the genes of embryos are manipulated will likely begin in the UK in 2017 (Callaway 2016).

The development of GE has been marred by controversy. Some public interest groups, including the United Nations Educational Scientific and Cultural Organization (UNESCO), have called for an international ban on any GE research in human embryos. The US-based National Institutes of Health maintained that performing such research would cross "a line that should not be crossed" (Collins 2015, 1). The major scientific journals *Nature* and *Science* have published commentaries, which call for this research to be strongly discouraged or stopped altogether (Lanphier et al. 2015; Baltimore et al. 2015).

While GE is controversial, other techniques that allow parents to influence the genetic makeup of their children are relatively common. Sperm banks and egg donation websites allow women and couples to pick and choose between different gamete donors based on a range of characters – and then create a child through in vitro fertilization (IVF) or artificial insemination. In the US alone, between 30,000 and 60,000 children are born through sperm donation each year and >8,000 from egg donation (Sabatello 2015). Preimplantation genetic diagnosis (PGD) allows embryos created through IVF to be tested for the presence or absence of genetic conditions,

before implantation. It is currently possible to use PGD to select against any one of nearly 400 conditions (Human Fertilisation and Embryology Authority [HFEA] 2017).

In this paper, I first introduce the range of "reproductive genetic technologies" (RGTs) – technologies that allow parents to influence the genetic makeup of their future children.[1] I then examine two ethical questions: (1) Assuming such technologies are safe and effective, do parents have reasons to influence the genes of their children? (2) If so, does the type of RGT they use matter, legally and morally?

1.2 Use of RGTs[2]

1.2.1 IVF and PGD as tools

The development of IVF in the 1970s marked an important milestone in human reproduction. For the first time in history, human embryos could be created outside the body of the mother. This innovation was followed in the early 1990s by PGD, in which the embryos created in vitro were tested for the presence or absence of particular genes (Theodosiou and Johnson 2011).

PGD was initially developed as an alternative to prenatal testing and selective abortion within a legally and medically defined boundary (Theodosiou and Johnson 2011). It allowed parents to create many embryos and test each for genes associated with serious disabilities. This allowed parents to avoid serious disability without the emotional and physical costs associated with abortion. However, the potential for IVF and PGD to be used for nonmedical purposes soon became apparent. Through IVF, it is possible for parents to choose between embryos based on the presence of genes associated with nonmedical traits, such as height or intelligence. In theory, choosing an embryo that is likely to be taller, for instance, comes at little extra cost to the mother (although regulations in many parts of the world prevent such nonmedical applications).

Many human traits have a strong genetic component and could thus potentially be targeted though PGD. Geneticists have already identified genes associated with height (Berndt et al. 2013), certain personality types (Jang et al. 1996), intelligence (Desrivières et al. 2015), and musical ability (Oikkonen et al. 2015). As our knowledge of genetics increases, it will likely become possible to perform quite sophisticated genetic analyses on embryos before implantation. Hence, IVF and PGD potentially provide parents with a mechanism to influence a great variety of traits in their children.

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1 This is independent of whether the identities of their children are also affected.

2 This section draws on my previous work: C. Gyngell and M. Selgelid. 21st Century Eugenics, In *The Oxford Handbook of Reproductive Ethics*, Leslie Francis (ed.) Oxford University Press (2016): 141–158.

1.2.2 Gamete screening

Gamete screening (GS) involves selecting between gamete donors, based on heritable characteristics. For decades, in countries such as the USA, individuals have been able to influence the genes of their children by using donated gametes (sperm and eggs) in combination with technologies such as IVF. Those using donated gametes often have access to detailed medical histories of the donors. Such individuals can not only reduce the chances of their children having a genetic disease but also choose donors with good medical histories. GS can not only be used to select against disabilities, it can also be used to select for nondisease traits such as eye color and height. Companies such as *Elite Egg Donors* allow prospective parents to choose between various gamete donors based on a wide variety of factors, including education, weight, and ethnicity.

While GS is currently relatively imprecise, new technologies that are likely to increase its power are being developed. In 2013, the genomics company '23andMe' received a patent for a technology called "Gamete Donor Selection Based on Genetic Calculations". While there are no suggestions that this technology is currently used, in the future, it would allow individuals accessing assisted reproductive services to choose between sperm or egg donors based on the statistical likelihood of the resulting child having a certain phenotype. Using 23andMe's technology, a woman wanting a blue-eyed child could select between different sperm donors to maximize this probability. She would differentially create an embryo with desirable characteristics, rather than selecting between different embryos or modifying an existing one.

1.2.3 Genetic engineering

In addition to being able to select between embryos based on their genetic makeup, parents may soon have the ability to directly modify embryos using genetic engineering technologies. Genetic engineering technologies potentially allow new genes to be inserted into embryonic DNA (Liang et al. 2015) and existing genes to be modified or deleted. These technologies could potentially be used to create much more significant changes in the traits of children than is possible through GS and PGD.

Genetic engineering technologies have been successfully used in other species to alter their physical, cognitive, and social characteristics. For example, in 2007, scientists at Case Western Reserve University used genetic engineering technologies to alter a gene called "PEPCK-A" in mice. The resulting transgenic mice could run for 6 km without a break – 30 times longer than a normal mouse's limit of 200 m. They also had extended life spans, compared to their unaltered counterparts, and retained the ability to breed well into old age (Hakimi et al. 2007). In 1999, scientists engineered mice to overexpress the gene "NR2B", which codes for a nerve cell receptor. This was shown to lead to dramatic improvements in memory, with transgenic mice being able to remember objects and experiences for many days longer than unaltered mice (Tang

et al. 1999). The social characteristics of some animals have also been altered using genetic engineering technologies. Polygamous voles can be turned monogamous by modifying genes associated with the vasopressin V1a receptor (Lim et al. 2004).

Early techniques relied on viruses to deliver novel genetic material to cells. This method was too ineffective and imprecise to have serious potential as a clinically useful modifying tool of human DNA. It often only changed one of the two copies of the target gene, meaning animals had to be bred together to make modifications effective. This method also made unintended changes to large segments of the genome, and only a small proportion of the modified animals did not suffer serious side effects.

Recently, a revolution in genetic engineering began. In 2012, a laboratory led by Jennifer Doudna and Emmanuelle Charpentier showed that a molecule used as part of the bacterial immune system could be used to edit DNA (Jinek et al. 2012). The CRISPR–CRISPR-associated protein (Cas)9 system contains two parts, a molecule that binds to particular DNA sequences (CRISPR) and an enzyme that cuts the DNA (Cas9). In a very short space of time, the GE technique CRISPR has been used to make precise and heritable changes to animals. It has been used to create malaria-fighting mosquitoes, drought-resistant wheat, hornless cows, and monkeys with targeted mutations. The potential applications of GE in a decade are difficult to imagine. Because of their increased precision, GE techniques are the first genetic engineering technologies to have serious potential to modify human DNA.

It is clear that germline GE holds tremendous potential in the fight against many types of diseases. Most immediately, GE could be used to correct mutations that cause simple genetic diseases, such as cystic fibrosis, muscular dystrophy, and Tay–Sachs disease. Currently, such diseases can largely be prevented through genetic selection technologies such as PGD (HFEA 2017). However, PGD has significant limitations. Its ability to avoid disease is directly related to the number of embryos that can be created through IVF. Sometimes, couples will produce only one or two embryos, in which case PGD will not be effective in avoiding even simple genetic diseases. GE can be used to make multiple changes to a single embryo. It is free of PGD's limitations and would be a more efficient way of preventing simple genetic diseases.

More significantly, GE's ability to make multiple changes to a single embryo means that, in the long term, it could be used to prevent a far greater range of diseases than PGD. Cancer, diabetes, and heart disease all have significant genetic components. It is at least conceivable that we could use GE to make us resistant to these diseases – which are among the leading cause of mortality worldwide (World Health Organization [WHO] 2017). Imagine a steroid injection was developed, which if taken by a woman while pregnant would change the in-uterine environment in such a way that the embryo becomes resistant to cancer and cardiovascular disease. Most would consider such an intervention to be a wondrous medical breakthrough, which should be provided to all. GE may make such an intervention a reality one day.

In the future then, it seems plausible that it will be technologically possible for parents to modify the DNA of embryos created through IVF. As genetic technologies

continue to advance, it may also become possible for embryos conceived naturally to be modified via vectors delivered directly to the uterus. This would not only provide a novel way for parents to be able to treat and prevent disease, it could also allow parents to influence a wide range of nonmedical characteristics of their children.

1.2.4 *In vitro* gametogenesis

Technologies that promise to greatly increase the selective power of IVF and PGD are currently being developed. In vitro gametogenesis (IVG) involves artificial production of germ cells (oocytes and sperms) from other cell types. It is now possible for embryonic murine and adult murine stem cells to be turned into sperm or egg cells in a Petri dish (Magnusdottir and Surani 2014). These cells are functional and have resulted in the birth of fertile offspring. This technology potentially allows any adult to generate thousands of germ cells from the stem cells contained in their bone marrow.

While most IVG research to date has been carried out in mice, there are several interesting possibilities for reproductive medicine in humans. The technique could one day allow people with no functional germ cells to produce children using standard IVF techniques. The technique could therefore have significant therapeutic benefits for those who are infertile.

In addition, the technique could greatly increase the selective power of IVF and PGD. The power of IVF is currently limited by the number of viable embryos a couple can produce (Bourne et al. 2012). Using IVG, any woman could potentially make hundreds or thousands of oocytes from her somatic cells. These could be used to make hundreds of embryos, all of which could undergo PGD. This would greatly increase the ability of IVF and PGD to be used to target polygenic traits – or multiple genetic traits at the same time. For example, imagine that 20 different genes contribute to a particular trait. If a couple aims to use PGD to select for 20 different alleles in an embryo, they would need to create around 10,000 embryos to make it sufficiently likely that one will have the desired combination at all 20 loci (Bourne et al. 2012). This is impossible through IVF and PGD today but could become possible in the future through IVG.

1.3 Should parents influence the genes of their children?

If these aforementioned technologies were safe, legal, and available to use on a developing embryo, would it be ethical to use them? I think it would be. I believe that we have strong moral reasons to use RGTs to protect future children from disease and suffering, such as those caused by single-gene disorders such as Tay–Sachs, spinal

muscular atrophy, cystic fibrosis, and so on. Changing your child's genes to improve their health is consistent with good parenting.

It is commonly accepted that we should prevent disease in our children through nongenetic methods. For example, we expect pregnant women to eat well during pregnancy and avoid risky behaviors, if this will benefit the health of future children. We think this even when their actions will change the identity of the child who is born – by changing which egg is fertilized by which sperm. To explain, take the following case, adapted from Derek Parfit (1992, 358). Imagine a woman who wants to have a child, but who has an infectious disease. If she gets pregnant while she has the disease, her child will have a serious birth defect. If she waits 6 weeks, until her disease has passed, her child will be healthy. Most would agree that, as a parent, individuals in this position have good reason to wait the 6 weeks, even though it changes the identity of the future child.

So it is clear that parents try to benefit their future children through nonenvironmental measures. Why would genetic measures be morally different? Indeed, it is possible that some prenatal supplements currently widely taken do in fact have a genetic effect. For example, many women take vitamin D supplements through pregnancy. This is believed to make the developing child more resistant to bone diseases such as rickets (Royal Children's Hospital [RCH] 2017). We generally think pregnant women who take vitamin D supplements are acting responsibly. But vitamin D may alter the genes of the developing child – by changing the way its genes are expressed (Bocheva and Boyadjieva 2011). We think that women should take vitamin D supplements in pregnancy; therefore, we think it is permissible to make some genetic changes to a developing child in order to improve their health.

GE technologies make a different sort of genetic change to an embryo than vitamin D supplements. They change the genetic sequence, rather than the way genes are expressed. However, suppose that we discover that vitamin D supplements actually did work by changing the genetic sequence of a developing embryo? Would this discovery mean that we should advise women to stop taking vitamin D supplements during pregnancy? I think not. What is important is that taking vitamin D supplements while pregnant protects the developing child from developing diseases later in life. The mechanism through which this is achieved is irrelevant.

Some argue that the fact that RGTs make heritable change means that parents should not use those (Lanphier et al. 2015). But it is unclear why the fact that a disease is heritable should provide reasons against correcting it. To see why, imagine a hypothetical genetic disease that causes a hole to develop in a baby's heart soon after birth. The condition is nearly fatal. A new treatment (T1) involves injecting enzymes directly in the heart after birth to prevent the hole from forming. This treatment cures 80% of cases and has a low risk of side effects.

There are no reasons why T1 is unethical. Indeed, it is a moral imperative to provide T1.

Now imagine that babies who will get this condition can be detected by an in-utero genetic test. Treatment T2 injects the exact same enzymes as T1 but does so at the

embryonic stage. This prevents the hole from forming in 80% of cases, and it has a low risk of side effects.

Are there any morally relevant differences between T1 and T2? The only difference between the treatments is that T2 is applied in utero and T1, soon after birth. This seems morally irrelevant. Imagine that we can only fund T1 or T2, and that T2 cures 85% of cases rather than 80% as in T1. In this case, it seems that we now have decisive reasons to prefer T2 over T1.

One might argue that the fact that T2 produces a heritable change, unlike T1, is morally relevant and counts against T2. I believe this reasoning is flawed. As T2 corrects the genes that cause this disease, individuals who have T2 will not be at risk of passing on the disease to their children. Individuals who get T1 remain at risk of having children with the same disease. This is an advantage of T2, not a cost.

It is possible to use genetic engineering technologies and other RGTs to make a small number of genetic changes to protect our children from disease. The total length of the human genome is >3 billion base pairs. In some cases, changing just one base pair in an embryo will prevent diseases later in life. This means that changing <0.0001% of your child's genome can protect him/her from a suffering. This seems clearly ethically justified.

Another objection to RGTs stems from the fact that they could be used not just to protect children from disease but that they also influence children's other traits. They could be used as a tool of enhancement, rather than just disease prevention. The ethics of enhancement are complex and have been discussed at length elsewhere (e.g., Buchanan and Brock 2007). I will take no stand on that issue in this chapter. But even if there is a sustained universal objection to human enhancement, this does not change the moral reasons we have for preventing disease. We could limit the use of RGTs to disease prevention, just as we currently do with PGD. Hence, there do seem strong moral reasons to use RGTs to change the genetic makeup of children in order to prevent disease.

1.4 Does the method matter?[3]

If the argument in the preceding section is accurate, parents have moral reasons to use RGTs in order to prevent disease. Does it matter, both legally and ethically, which RGT they use? Is the use of GS ethically the same as selection or GE?

If we just look at the legal status of these technologies, it looks as if there are significant differences. GS is widely unregulated. Companies such as Elite Egg Donors (discussed earlier) have clinics in diverse countries, such as Mexico, Barbados,

3 This section is adapted from a short article that I wrote for *The Conversation*. Refer C. Gyngell. If you can screen for brown eyes, you should be able to edit out genetic disease. *The Conversation* July 11, 2016. Available at https://theconversation.com/if-you-can-screen-for-brown-eyes-you-should-be-able-to-edit-out-genetic-disease-61927.

California, and Nepal (*Elite Egg Donors* website http://eliteeggdonors.com/ 2017). In 2015, the London Sperm Bank was criticized for its decision to ban sperm donors who suffer from minor neurological disorders, including dyslexia and Asperger syndrome. Not only can GS be used to select against mild disabilities such as dyslexia, it can also be used to select for nondisease traits such as eye color and height.

PGD is far more widely regulated than GS. In many parts of the world, PGD is limited to the prevention of disease. For example, in the UK, regulations limit PGD to being used to select against "serious" inherited conditions. However, what is regarded as "serious" is considered on a case-by-case basis. Each proposed use of PGD is examined individually. Those that are risky or frivolous can be rejected.

The reproductive use of GE is widely banned around the world (including in the UK, Australia, Canada, Mainland Europe, and Japan (Isasi et al. 2016) either through legislation or best practice guidelines. Such bans make sense considering that GE technologies are so new and are only now beginning to be used in animal and somatic cells. There may still be consequences of GE that we do not understand, and much more research into the safety of genome editing needs to be performed before it is considered for reproductive use. It is important to note that such laws do not just ban unsafe uses of GE technologies – but any use. GE is developing rapidly. At some point, GE technologies are likely to be widespread, cheap, safe, and precise. If GE becomes a safe technology, will it be ethically different from other RGTs?

It seems inconsistent to hold that the *method* we use to select for or against an inherited condition should make such a significant difference to its legal status. A woman wanting to have a green-eyed child with blond hair, low predisposition to obesity, and high intelligence is legally able to use GS to choose among potentially thousands of donors, based on which of the donors is most likely to give her the child she desires. Conversely, a couple who wants to use GE technology to save their child from developing Tay–Sachs disease – a degenerative disease that results in death by the age of 3 years, cannot do so – even if it is the only way they could avoid the disease. This does not seem to track the ethical reasons at play in this comparison. It seems far more ethically permissible to avoid a lethal disease than avoid a particular eye color. When it comes to avoiding disease, there seems to be little moral difference between using different RGTs. This should be reflected in regulation. What we need then is a consistent approach to the regulation of inheritance, and PGD should serve as the model. Each proposed use of GS and GE should be assessed on a case-by-case basis. When therapies are shown to be safe and effective, they should be added to a list of approved conditions.

1.5 Conclusion

Parents have good reasons to provide benefits for their future children, even when this benefit will change the identity of their future children. There are no reasons

why this general principle should not also apply to RGTs. Parents have good reasons to benefit their future children through RGTs, particularly when they can be used to prevent devastating diseases. When it comes to avoiding disease, the choice of RGT is irrelevant – what matters is choosing genes that will benefit your children.

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