Published in *Genes for Life* in 2017 by Future Leaders (www.futureleaders.com.au)

The simple case for germline gene editing

Christopher Gyngell and Julian Savulescu

For over three decades, scientists have had the ability to alter the genomes of other species of animals. Using viruses to alter DNA sequences, scientists were able to create a range of transgenic animals — with altered physical, cognitive and social characteristics. In 2007, scientists at Case Western Reserve University used viruses to alter a gene called *PEPCK-A* in mice. The resulting transgenic mice could run for six kilometres without a break — 30 times longer than a normal mouse's limit of 200 metres (Hakemi et al., 2007). In 1999, scientists modified the cognitive capacities of mice by engineering them to overexpress the gene *NR2B*, which codes for a nerve cell receptor (Tang et al., 1999). These transgenic mice were able to remember objects and experiences for many days longer than unaltered mice. In 2004, scientists used viral vectors to modify genes associated with the vassopressin V1a receptor in prairie voles (Lim et al., 2004). This normally polygamous species was turned monogamous by the intervention.

Despite these impressive achievements, early modes of genetic engineering were imprecise and inefficient. They were inefficient, because the target sequences were only correctly modified in a small proportion of cases. As a result, many animals had to be experimented on for only a few to acquire the desired alteration. They were imprecise, because in addition to

causing the target sequence to change, they would also cause a number of other changes in the genome, called 'off-target' mutations. Many animals therefore suffered from unwanted side effects. As a result, these technologies never had serious potential to be a clinically useful modifier of human DNA.

The last few years has seen the development of a number of efficient, more precise genetic engineering techniques. These techniques have been given the collective name 'gene editing technologies', to reflect their increased accuracy over previous methods. The most powerful gene editing technology is the CRISPR-cas9 system. CRISPR cas-9 consists of two parts, a DNA cutting enzyme (the cas9 part), and a guide sequence (the CRISPR part). When the guide DNA binds with a complementary DNA sequence in the cells it enters, it triggers the cas9 enzyme to cut, making a double-sided break to the DNA sequence. CRISPR-cas9 is used by bacteria as a defence against viruses, cutting viral DNA into small, non-functional fragments. In 2012, a team at UC Berkeley showed that CRISPR-cas9 could be modified in the lab so that it could target virtually any DNA sequence (Jinek et al., 2012). This allowed researchers to cut DNA virtually anywhere in the genome. Furthermore, they demonstrated that after the DNA was broken, DNA repair mechanisms could be recruited to add novel genetic material to the site of break. This gave researchers the ability to delete, add, or modify DNA sequences.

In April 2015, it was announced that CRISPR had been used for the first time to make edits in human embryos. This was the first instance of what we will call human germline gene editing (GGE).[1] The study, conducted in China, targeted the gene responsible for producing part of the haemoglobin molecule — with mixed success (Liang et al., 2015). In February 2016, the United Kingdom became the first country to officially approve gene-editing research in human embryos.

One of the greatest mysteries in life is why only about one in three embryos formed naturally ever go on to produce a baby. Most miscarry. By genetically engineering human embryos, scientists in the United Kingdom reported in September 2017 that they had identified a key gene in early human development. Kathy Niakan, of the Francis Crick Institute in London, led a team that used the gene-editing technique CRISPR-CAS9 to investigate the role of a particular gene (*OCT4*) in embryonic development. The study could potentially lead to better understanding of miscarriage, and hopefully prevention of it, and improve treatment of infertility (Fogarty et al., 2017).

Some public interest groups, including the United Nations Educational Scientific and Cultural Organization (UNESCO) have called for an international ban on any gene-editing 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). The major scientific journals *Nature* and *Science* have published commentaries that call for this research to be strongly discouraged or stopped altogether (Lanphier et al., 2015).

While gene editing is controversial, other techniques that allow parents to influence the genome of their future children are relatively widespread and accepted. Sperm banks and egg donation websites allow women and couples to select among different gamete donors based on a range of characteristics — and then create a child through in-vitro fertilization (IVF) or artificial insemination. In the United States alone, between 30,000–60,000 children are born through sperm donation each year and over 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. In the United Kingdom, PGD has been approved for over 250 conditions.

As a result of the rapid development of gene editing technologies, governments around the world need to examine their regulatory frameworks for reproductive technologies. The ethical implications of GGE must be a key input to these considerations. Here, we outline a simple moral case for pursuing GGE. First, we review the regulatory status of GGE around the world. Then we outline the moral reasons in favour of GGE. We show there is a strong *pro tanto* case for pursing gene editing; for both its immediate utility in research and short and long term potential in therapy. Finally, we consider some of the ethical issues that have been used to argue against gene editing. We argue that none of these count decisively against gene editing. In our conclusion, we argue that there is a need for global regulatory reform to accommodate GGE.

Current regulations

Currently, GGE is highly restricted through legislation or through guidelines. This is in contrast to other reproductive technologies like PGD. Many of the 29 countries with bans on GGE allow PGD to prevent genetic disease (Isasi, Kleiderman, & Knoppers, 2016).

Of those countries in which GGE is banned, we can make a distinction between those that ban both research and reproductive application of GGE, and those that only ban reproductive uses.

For example, in the United Kingdom, it is permitted to use GGE in research in gametes and in embryos up to 14 days. However, all reproductive applications are banned. Likewise, Finland allows research 'to modify hereditary properties is permitted if the research is aimed at curing or preventing a serious hereditary disease' (Araki & Ishii, 2014).

It is also important to note that (as far as we can tell) all countries that have banned GGE in research make no distinction

between research involving gametes (sperm and egg), and those involving human embryos. Many jurisdictions (including Japan) specifically ban the editing of both gametes and embryos. Others just refer to banning 'germline' or heritable modifications.

The case for gene editing

Therapy

Many diseases have a simple genetic mechanism, or are strongly influenced by genes. The development of gene editing could be a vital tool in our fight against disease.[2]

The most straightforward clinical use of GGE will be in the treatment of simple Mendelian disorders such as Tay Sachs disease, Duchenne muscular dystrophy, cystic fibrosis, and spinal muscular atrophy. These conditions are caused by well-understood genetic pathways, and can have a significant impact on life expectancy. We currently use PGD to prevent these conditions, but PGD is not always an effective treatment. When IVF only produces a small number of viable embryos, selection is not possible. Furthermore, PGD cannot be used to prevent diseases that are due to *de novo* mutations; that is, those that occur in the egg or sperm but are not inherited. In some cases, using GGE will be the only way that individuals can avoid fatal disease in their children.

Many object that such cases are rare and that PGD is effective in the clear majority of cases. But even if such cases are rare, we still have moral reason to try to prevent them. There are strong *pro tanto* moral reasons to cure rare diseases, and there are strong *pro tanto* moral reasons to prevent rare genetic conditions. While we need to consider the number of people who will benefit from a treatment when making policy decisions, the fact that a disease is rare does not alter the moral valence of preventing it.

Furthermore, even when selection can be used to avoid disease, GGE may provide a more desirable option. Selection prevents disease by changing who comes into existence; whereas gene editing ensures those who come into existence have the best shot of living a full life. Using GGE to avoid disease thus seems more analogous to curing a disease than PGD.

GGE may also be preferable than PGD because of its greater potential to reduce rates of genetic diseases in the next generation. PGD is often not used to select against carriers of a condition, partly because this is difficult to achieve with the number of embryos couples typically produce through IVF. GGE provides a way to remove all disease-causing genes from an embryo or gamete. Using GGE to prevent single gene disorders will thus provide a more effective way to reduce the incidence of these diseases in future generations than PGD.

In the future, GGE could also be a vital tool in the fight against polygenic diseases. Approximately 30% of all deaths worldwide are caused by chronic disease (e.g. diabetes, cancer and heart disease) in those under 70 (WHO, 2017). Such diseases are the result of genetic predispositions in combination with environmental influences. The sheer number of genes involved in these disorders means that PGD could never be used to prevent them. For example, genome-wide association studies have identified at least 44 genes involved in diabetes (Wheeler & Barroso, 2011); 35 genes involved in coronary artery disease (Peden & Farrall, 2011); and over 300 genes involved in common cancers (Chang et al., 2015). Say a couple want to use PGD to select for 20 different genes in an embryo. Then they would need to create around 10,000 embryos to make it sufficiently likely that one will have the right combination at all 20 loci. The chance of the couple having such a child would be just approximately 0.01% with traditional IVF and PGD (Bourne, Douglas, & Savulescu, 2012).

GGE allows multiple changes to be made to a single embryo, and could therefore target many different genes simultaneously. GGE could provide a vital tool in the fight against chronic diseases like cancer, diabetes and heart disease.

Research

GGE is a very young technology. It should only be used for the above therapeutic purposes if it is shown to be safe through research. GGE is like all other medical technologies in this regard. The central question currently facing governments around the world with regard to GGE is not whether GGE should be used for therapy, but whether it should be permitted in research.

Of course, given there is a strong therapeutic case for GGE, it follows that there is a strong case for GGE research. Just as we have reasons to conduct medical research that may one day lead to a cure for disease, we have reason to conduct research aimed at improving GGE so that it may one day be used in the treatment for disease.

Furthermore, there may be other reasons why research using GGE is important.[1] Editing human embryonic stem cells could be a breakthrough for the study of early human development, as we saw previously. We still have a poor understanding of many events that happen in early development. Only about one-third of embryos conceived naturally ever go on to form a baby, and 5% of these individuals have a significant problem in childhood. Using GGE to investigate the activity of specific groups of genes allows researchers to better understand the processes that drive development. Improving our knowledge of development will help provide better cures for infertility and reduce miscarriage.

In sum, there are *pro tanto* moral reasons in favour of allowing GGE — both for its immediate utility in research and its short and

long-term potential in therapy. For current legislative bans on GGE to be justified on moral grounds, there must be significant moral reasons against its use in research or reproduction.

The case against gene editing

Use of embryos

Some believe we should not allow GGE because of concerns about the moral standing of early human embryos.[3]

The moral status of early human embryos is the subject of a long and complex philosophical debate. Some believe that embryos have the same moral status as persons. But this position is widely inconsistent with how other accepted technologies are regulated. Many jurisdictions permit embryo research that involves the destruction of the embryo for research aimed at improving fertility. Similarly, many jurisdictions allow destructive forms of contraception, such as intrauterine devices (IUD) and oral contraceptives, abortion and the destruction of unwanted IVF embryos. It is doubtful that one could hold these practices to be permissible — as many do — while holding that the death of even an early embryo counts as much morally as a person's death (Douglas & Savulescu, 2009).

Furthermore, even if we assume that early human embryos do have a high moral status, this does not count against all forms of GGE research. Much GGE research could be done entirely on gametes. For example, researchers could attempt to edit the gene that causes cystic fibrosis, *CFTR*, in spermatogonial stem cells and derive sperm carrying the corrected gene. Research could one day lead to ways to avoid cystic fibrosis without PGD, and the necessary loss of embryos this entails.

Therefore, even if we assume early human embryos have a high moral status, this does not generate reasons against GGE — but rather suggests its development should be conducted in ways that minimise the loss of embryos.

Non-interference

Some arguments against GGE focus not on its use in research, but its use in reproduction. Some think that any moral reasons against GGE in reproduction leads to reasons against its use in research, as they believe that GGE research will inevitably lead to reproductive applications. We have argued previously that this assumption is flawed, as the case of PGD shows.[1] However, here we will assume for the sake of argument that we could not limit GGE to research and therefore that arguments against the reproductive uses of GGE also generate arguments against its use in research.

A group of arguments against the reproductive use of GGE centre on the principle of non-interference. They argue that there is no justification for altering embryos in ways that make significant changes to their characteristics. Just as it is wrong to change someone's eye colour without their consent, it is wrong for me to change the colour of my future children's eyes through GGE. On some views, such acts are wrong as they disrupt my future child's autonomy; or, because of my decisions, expresses a dominating attitude toward my child.

One could accept that some form of a non-interference principle operates over embryos, yet still be in favour of GGE. This is because one could deny that non-interference principles apply to gamete cells. Hence, it is consistent to accept some form of non-inference principle and still be in favour of GGE applications. Hence, as was the case regarding the use of embryos, the existence of non-interference principles does not necessarily count against GGE, but merely should suggest it should be developed in a certain way.

Furthermore, it is doubtful that such a principle should be considered to apply to human embryos. While non-interference principles seem plausible between strangers, they are very

strange in the context of parent-child relationships. Parenting is all about interferences. Parents make constant decisions about which dispositions, skills and traits they wish to cultivate in their children. In cultivating particular dispositions and traits in their children, parents are constantly making decisions that have lasting effects on their children and that cause them to develop in particular ways.

Some resist this comparison because they think that environmental influences should be distinguished from genetic ones.[4] However, a distinction between environmental and genetic influences is difficult to draw. Many common parenting practices affect the genes of their children. For example, the particular diet a child eats has epigenetic effects, and therefore changes how a child's genes are expressed (Hardy & Tollefsbol, 2011). Similarly, other parenting practices are also likely to result in epigenetic modifications. Indeed, many health guidelines recommend that mothers expose their children to epigenetic modifiers before they are born. Many women are instructed to take vitamin D supplements through pregnancy. Vitamin D is an epigenetic modifier that is believed to make the developing child more resistant to a bone disease like rickets, and immune diseases like asthma and multiple sclerosis. Recent research indicates vitamin D may alter the genes of the developing child (Bocheva & Boyadjieva, 2011). If we think women should take vitamin D supplements in pregnancy, we therefore think it is okay to make some genetic changes to a developing child. This counts against the plausibility of non-interference principles that apply to developing embryos.

Most importantly, non-interference may have some plausibility in relation to non-disease traits, but it has no plausibility in relation to gene editing of disease. Gene editing is a form of 'ultimate cure' for disease: it treats disease at its very root. For

example, an enzyme replacement therapy can now prevent the severe manifestations of the genetic disorder Gaucher disease. The enzyme, glucocerebrosidase, replaces the enzyme not produced by the body because of a genetic mistake. Gene editing would simply correct this mistake and allow the body itself, rather than a pharmaceutical company, to make this enzyme. Curing disease is just the kind of interference medicine aims at.

Justice

A common concern about GGE is that it is unjust.[5] For example, McKibben (2003) states:

> These would be mere consumer decisions — but that also means that they would benefit the rich far more than the poor. They would take the gap in power, wealth, and education that currently divides both our society and the world at large, and write that division into our very biology.

Technologies like GGE may provide greater benefits to those who are already well-off and increase fundamental inequalities.

However, even if we assume that everything McKibben states is correct in regards to GGE — it does not necessarily imply that GGE is unjust. Under many theories of justice, developments can still be just even if they increase the gap between rich and poor. The only view of justice under which increasing the gap between rich and poor is necessarily unjust is strict egalitarianism — which is the view that medical resources should be distributed with the goal of minimising inequality — either economic inequality or inequalities in wellbeing.

However, egalitarianism has been shown to have highly counter-intuitive implications, and is widely held to be an implausible principle of distributive justice in political philosophy. For example, consider the following two outcomes[6] where

the numbers represent units of wellbeing, or some important resource.

	Group 1	Group 2
Outcome 1	9	9
Outcome 2	99	100

If we adopt an egalitarian position, we should see outcome 1 as the superior outcome, as there is no inequality between the members of Group 1 and Group 2.

This result seems clearly wrong. Everyone in Outcome 2 is much better off than in Outcome 1, and there is only very minor inequality. Imagine we are in a society that has a distribution as in Outcome 1, and we have the option of moving to Outcome 2. In essence, we have the option of making everyone much better off, but some slightly more so than others. Egalitarians would claim that this move is undesirable. This is highly counter-intuitive and casts significant doubt on strict egalitarianism as a theory of justice.

Furthermore, there are ways that GGE may help remedy existing injustices. The most obvious way in which GGEs will remedy injustice is by reducing rates of disease. Many diseases are caused only by quirks of our biology. Some people randomly develop diseases, while others do not. They can cause pain, reduce lifespan, and limit one's ability to pursue one's goals. Diseases can also impose a significant financial cost on sufferers and their families, and thus contribute to economic inequalities. But by reducing rates of genetic disease, GGE could help remedy these forms of biological injustice.

In the future, GGE could also help remedy social injustice by providing a way to reduce the incidence of polygenic diseases. Low socioeconomic status is associated with increased risk of a range of disease, including cardiovascular disease, diabetes and arthritis. As those in lower socioeconomic groups are generally

worse off than those in higher groups, these diseases place an additional burden on those who are already the worst off.

For example, a lower socioeconomic status is associated with a 55% increase in heart disease in men and greater than twofold risk increase in women (Clark et al., 2009). This is likely explained by a range of environmental risk factors that those in lower socioeconomic groups are more likely to be exposed to, including poor diet, smoking and a lack of access to medical care. Heart disease, therefore, exacerbates existing social inequalities. In the future, GGE could lead to novel treatments for heart disease, and therefore they can be seen to remedy this injustice.

Furthermore socio-economic status also influences access to medical care. While those in high socio-economic groups often have the financial resources to purchase good medical care for themselves, those in lower groups must depend on public health systems. If we could improve the efficiency of public health systems, we would improve access to medical care for those in lower socioeconomic groups and promote equality of access to medical care.

For example, as we have discussed, Gaucher disease is caused by a genetic defect that results in the reduction/absence of the enzyme glucocerebrosidase.[7] It can result in disease affecting the liver, spleen, lungs and kidneys and can be lethal. Fortunately, there is an effective treatment. A modified version of the enzyme can be produced in the laboratory and administered directly into a patient's bloodstream.

Many will say that as we already have a treatment for disease like Gaucher disease, we do not need additional therapies made possible through GGE. However, this view is shortsighted. The cost of treating each patient with Gaucher's disease ranges between $200,000 and $400,000 per patient year per person (Dussen et al., 2014). Over a patient's lifetime the cost is

approximately $9 million. This is many times above the cost effectiveness threshold used by many public health systems (such as the Australian health system and United Kingdom's National Health Service) but in many cases it is still covered as an 'orphan' drug.

In public health systems with limited resources, an expensive therapy has the opportunity cost of preventing the treatment of someone else's disease. Justice requires we choose the most cost-effective option. GGE could potentially cure Gaucher disease in one treatment. The cost would possibly be in the range $10,000 in total per person, compared with $9 million lifetime of treatment through enzyme replacement. The development of a cheaper treatment for Gaucher disease would increase the efficiency of public health systems and allow more diseases to be treated. This would disproportionately benefit those in lower socio-economic groups — who rely more on public health systems. This is another way GGE can remedy existing injustices.

Conclusion

GGE is highly restricted around the world, including in research. Such laws are not justified by the moral implications of GGE. There is a simple moral case for allowing GGE — it has immediate utility in research and both short- and long-term potential in therapy. While certain moral arguments have been introduced against GGE, none of these count decisively against it. Rather, these concerns suggest that GGE should be developed in certain ways. Governments around the world need to radically shift their regulatory approach to GGE. At the very least, research into GGE ought to be permitted even if at this stage we ban GGE to produce babies because the science is in its infancy. But if the science progresses, we would have the same

moral obligation to employ GGE as we have to employ any other cure for disease.

Endnotes

1 By germline, I mean the DNA in cells which could potentially be heritable.

2 I have previously pursued this argument in favour if gene editing in Savulescu, J., & Gyngell, C. (2015), The medical case for gene editing. *Ethics in Biology, Engineering and Medicine, 6*, 57–66, doi:10.1615/EthicsBiologyEngMed.2015014314; Gyngell, C., Douglas, T., & Savulescu, J. (2016). The ethics of germline gene editing. *Journal of Applied Philosophy,* doi:10.1111/japp.12249.

3 See, for example, MacKellar, C. (2017). Gene editing of human embryos — more ethical questions to answer. *Bionews.* Retrieved from http://www.bionews.org.uk/page_523365.asp

4 See, for example, Gheaus, A. (2016). Parental genetic shaping and parental environmental shaping. T*he Philosophical Quarterly, 67*, 263–281. doi:10.1093/pq/pqw064

5 I have previously considered these issues in relation to IPS cells. See Gyngell, Savulescu, and Crisp (forthcoming).

6 These cases are taken from Crisp, R. (2003). Equality, priority, and compassion. *Ethics, 113*, 745–763. doi:10.1086/373954

7 This example was originally suggested to me by Julian Savulescu.

References

Araki, M., & Ishii, T. (2014). International regulatory landscape and integration of corrective genome editing into in vitro fertilization. *Reproductive Biology and Endocrinology, 12*, 1–12. doi:10.1186/1477-7827-12-108

Baltimore, D., Berg, P., Botchan, M., Carroll, D., Alta Charo, R., Church, G., Corn, J.E., … Yamamoto, K.R. (2015). Biotechnology: A prudent path forward for genomic engineering and germline gene modification. *Science, 348*, 36–38. doi:10.1126/science.aab1028

Bocheva, G., & Boyadjieva, N. (2011). Epigenetic regulation of fetal bone development and placental transfer of nutrients: Progress for osteoporosis. *Interdisciplinary Toxicology, 4*, 167–172. doi:10.2478/v10102-011-0026-6

Bourne, H., Douglas, T., & Savulesc, J. (2012). Procreative beneficence and in vitro gametogenesis. *Monash Bioethics Review, 30*, 29–48.

Chang, C.Q, Yesupriya, A., Rowell, J.L., Pimentel, C.B., Clyne, M., Gwinn, M., Khoury, M.J., Wulf, A., & Schully, S.D. (2014). A systematic review of cancer GWAS and candidate gene meta-analyses reveals limited overlap but similar effect sizes. *European Journal of Human Genetics, 22*, 402–408.

Clark, A.M., DesMeules, M., Luo, W., Duncan, A.S., & Wielgosz, A. (2009). Socioeconomic status and cardiovascular disease: Risks and implications for care. *Nature Reviews Cardiology, 6*, 712–22. doi:10.1038/nrcardio.2009.163

Collins, F. (2015). Statement on NIH Funding of Research Using Gene-Editing Technologies in Human Embryos. National Institute of Health.

Douglas, T., & Savulescu, J. (2009). Destroying unwanted embryos in research. Talking point on morality and human embryo research. *EMBO Reports, 10*, 307–312. doi:10.1038/embor.2009.54.

Fogarty, N.M.E., McCarthy, A., Snijders, K.E., Powell, B.E., Kubikova, N., Blakeley, P., … Niakan, K.K. (2017). Genome editing reveals a role for OCT4 in human embryogenesis. *Nature.* doi:10.1038/nature24033

Gyngell, C., & Savulescu, J. (2015). The medical case for gene editing. *Ethics in Biology, Engineering and Medicine, 6*, 57–66. doi:10.1615/EthicsBiologyEngMed.2015014314

Gyngell, C., Douglas, T., & Savulescu, J. (2016). The ethics of germline gene editing. *Journal of Applied Philosophy, 34*, 498–513. doi:10.1111/japp.12249

Hakimi, P., Yang, J., Casadesus, G., Massillon, D., Tolentino-Silva, F., Nye, C.K., … Hanson, R.W. (2007). Overexpression of the cytosolic form of phosphoenolpyruvate carboxykinase (GTP) in skeletal muscle repatterns energy metabolism in the mouse. *Journal of Biological Chemistry, 282*, 32,844–32,855.

Hardy, T.M., & Tollefsbol, T.O. (2011). Epigenetic diet: Impact on the epigenome and cancer. *Epigenomics, 3*, 503–518. doi:10.2217/epi.11.71

Isasi, R., Kleiderman, E., & Knoppers, B.M. (2016). Genetic technology regulation. Editing policy to fit the genome? *Science, 351*, 337–339. doi:10.1126/science.aad6778

Jinek, M., Chylinski, K., Fonfara, I., Hauer, M., Doudna, J.A., & Charpentier, E. (2012). A programmable dual-RNA-guided DNA

endonuclease in adaptive bacterial immunity. *Science, 337*, 816–821. doi:10.1126/science.1225829

Lanphier, E., Urnov, F., Ehlen Haecker, S., Werner, M., & Smolenski, J. (2015). Don't edit the human germ line. *Nature, 519*, 410–411. doi:10.1038/519410a

Liang, P., Xu, Y., Zhang, X., Ding, C., Huang, R., Zhang, Z., … Huang, J. (2015). CRISPR/Cas9-mediated gene editing in human tripronuclear zygotes. *Protein & Cell, 6*, 363–372. doi:10.1007/s13238-015-0153-5

Lim, M.M., Wang, Z., Olazabal D.E., Ren, X., Terwilliger, E.F., & Young, L.J. (2004). Enhanced partner preference in a promiscuous species by manipulating the expression of a single gene. *Nature, 429*, 754–757.

McKibben, B. (2003). Designer genes. *Orion Magazine.* Retrieved from www.orionmagazine.org/index.php/articles/article/

Peden, J.F., & Farrall, M. (2011). Thirty-five common variants for coronary artery disease: The fruits of much collaborative labour. *Human Molecular Genetics, 20*, R198–205. doi:10.1093/hmg/ddr384

Sabatello, M. (2015). Regulating gamete donation in the U.S.: Ethical, legal and social implications. *Laws*, *4*, 352–376. doi:10.3390/laws4030352

Tang, Y.P., Shimizu, E., Dube, G.R., Rampon, C., Kerchner, G.A., Zhuo, M., Liu, G., & Tsien, J.Z. (1999). Genetic enhancement of learning and memory in mice. *Nature, 401*, 63–69.

Van Dussen, L., Biegstraaten, M., Hollak, C.E.M., & Dijkgraaf, M.G.W. (2014). Cost-effectiveness of enzyme replacement therapy for type 1 gaucher disease. *Orphanet Journal of Rare Diseases*, *9*, 51. doi: 10.1186/1750-1172-9-51.

Wheeler, E., & Barroso, I. (2011). Genome-wide association studies and type 2 diabetes. *Briefings in Functional Genomics*, *10*, 52–60. doi:10.1093/bfgp/elr008

World Health Organization. (2017). Chronic diseases and health promotion. Retrieved from http://www.who.int/chp/en/