Gene editing and the health of future generations[i]

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The CRISPR-cas9 gene editing system (CRISPR) is a revolutionary technology that promises unparalleled abilities. It is the first technology that allows for the precise, efficient modification of DNA sequences. Less than five years since it was first developed, it has been used to alter a diverse range of organisms, including plants, livestock, insects, and primates. There is little doubt that it will soon be technically possible to use the CRISPR system to rewrite the human genome. It is crucial that we consider the impact such technologies will have on future generations. The ability to alter our biological makeup will create immense opportunities but also pose novel threats. It is crucial that we make sensible decisions about the development and use of gene editing technologies.

In this commentary, I discuss the effect that germline gene editing (GGE)[ii] will have on the health of future generations. I argue that provided GGE is well regulated, it could greatly improve the health of our descendants. The use of GGE in research will greatly increase our knowledge of development and could lead to novel treatments for disease. GGE also has enormous potential as a clinical tool. It could soon be used to prevent simple genetic diseases; and eventually to reduce the incidents of polygenic diseases. While the use of GGE to prevent disease raises contentious philosophical issues, conceptual uncertainty should not holt the development of GGE as a research tool and a treatment for fatal genetic conditions.

The research applications of GGE

The most significant question currently facing counties in regards to GGE is whether to use GGE for research purposes. In many countries around the world, such as Canada, Australia and most of Europe, any form of research using GGE is banned. Many of these bans were legislated in eras of far cruder genetic engineering technologies. Gene editing techniques like CRISPR-cas9 are much more precise and efficient than previous methods; and are the first technologies with serious potential to be used to modify the human germline.

The research case in favour pursuing GGE is very strong.[1] Editing human embryonic stem cells (ES cells) could be a breakthrough for the study of early human development. Many theories regarding how many events happen in early development are based on mice models, which are proving to be unreliable.[2] Early human development remains largely a mystery. 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 of infertility. Less than a third of fertilized embryos survive pregnancy.[3] We have a poor understanding of why this is. Using GGE to study early development could lead to a great understanding of the causes of infertility and to better treatment options.

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[i] This article builds from arguments I presented in a debate at the Royal Society for Medicine event "Gene editing in medicine: breakthrough or thin edge of the wedge?"

[ii] By 'germline' gene editing, I mean the editing of DNA in cells which could potentially be heritable e.g. germ cells or embryonic cells.

GGE can also improve our understanding of genetic diseases. Gene editing allows researchers to generate ES cell lines with different specific disease alleles on the same genetic background.[4] Such cell lines can be used for the study of genetic disease. For example, the CRISPR system could be used to alter ES cells to contain mutations associated with Parkinson's disease. These cells could then be induced to grow into nerve cells (which malfunction in Parkinson's disease). These nerve cells could be used for the detailed study of the mechanisms involved in Parkinson's disease, and serve as a platform to test potential treatments. GGE could thus expedite the development of pharmacological therapies for genetic diseases.

While such research can be performed using induced pluripotent stem (IPS) cells, ES cells may have technical advantages.[5] IPS cell models are created from somatic cells, which may have undergone epigenetic changes. As a result, IPS cells may be more diverse and behave less predictably than ES cells in certain applications.

The use of GGE in research, therefore, could improve the health of future generations. By providing a new way to study human development, GGE may lead to better treatments for infertility. Furthermore, GGE could be used to create cellular models and further our understanding of genetic disease. Such knowledge may be valuable in its own right, in addition to leading to treatments for serious disease.

Single gene disorders

Beyond research, it may soon be feasible to use GGE in human reproduction. The most obvious clinical use of GGE will be to correct the mutations associated with fatal single gene disorders such as Tay Sachs disease, Duchenne muscular dystrophy, cystic fibrosis, and spinal muscular atrophy. These conditions are caused by well understood genetic mechanisms, and can reduce life expectancy by decades. We currently use genetic selection techniques like preimplantation genetic diagnosis (PGD) to reduce the incidence of these conditions, but PGD is not always effective. When IVF only produces a small number of viable embryos, selection is not possible. Furthermore, PGD is useless to those who are homozygotes for dominant conditions like Huntington's disease. In these cases, using GGE will be the only way that individuals can avoid serious disease in their children.

Many object that such cases are rare, and that PGD is effective in the vast majority of cases. But even when selection can be used to avoid disease, GGE may provide the more desirable option. PGD involves creating a number of embryos, testing each, and then only implanting those most likely to be healthy. PGD nearly always results in embryos being discarded. For some, this is an undesirable feature of PGD, which GGE can avoid.[iii] Furthermore the way in which GGE avoids disease may be preferable to PGD. 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.

Furthermore GGE, may be more preferable than selection in the treatment of single gene disorders because of its 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. In the case of autosomal recessive disorders, children who are born as the result of PGD are likely to be carriers of condition their parents selected against. GGE will provide a way to remove all disease causing genes from an embryo, and so the germ cells in that embryo will not carry the mutation.

[iii] Such benefits largely depend on GGE developing the point where it is efficient enough to be used on a single embryo.

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.

Chronic diseases

In the far future – perhaps in a few decades – we may be in a position to use embryonic gene editing to target other causes of death. Roughly 30% of all deaths worldwide are due to chronic diseases (such as heart disease, cancer, and diabetes) in those under 70.[6] Many billions of dollars are spent each year trying to develop new treatments to these disorders and reduce their impact on mortality. We know that chronic disease is affected by our genetic make-up. For example, genome-wide association studies have identified at least 44 genes involved in diabetes;[7] 35 genes involved in coronary artery disease;[8] and over 300 genes involved in common cancers.[9] As we understand more about genetics, and more about the aetiology of these disorders; it will be possible to reduce our susceptibility to these diseases. The ability of GGE to target multiple genes simultaneously means it could potentially be used to reduce the incidence of these disorders.

Disability, diversity and risks to human health

As the above section argues, it is clear that GGE could be used to reduce genetic disease. But this raises the question - how far to do we go? Do we use GGE to target all diseases – all undesirable traits? Such questions are complex and controversial. A common theme of the disability pride movement is that our common-sense views of disability are mistaken. Many of the conditions that we view as diseases and disability are not, in fact something bad, but rather something to take pride in. This presents a worry. If GGE is used to eradicate conditions that are in fact not negative, this will not improve the health of future generations at all.

Worse, if we use GGE overzealously, it may harm future generations, by removing valuable forms of human diversity.[10] Human groups benefit from certain types of diversity, including immuno-diversity (diversity in the genes that influence innate immunity) and cognitive diversity (diversity in the genes that affect our cognitive traits). It is plausible that some conditions we think of as diseases may contribute to valuable forms of diversity. For example, its plausible that Asperger's syndrome and dyslexia are sources of valuable forms of cognitive diversity.[11] Similarly, conditions like deafness which cause people to experience the world in unique ways, may also contribute to valuable forms of diversity.

These questions are difficult and complex. It is the subject of intense debate in philosposphy how to distinguish healthy forms of human diversity from disease and disability. However, we should not let this conceptual uncertainty be barrier to the development of GGE.

As noted above GGE is valuable as a research tool; independent of whether it is ever used in a clinical setting. Furthermore even if some diseases and disabilities may be valuable forms of diversity, many are clearly not. No one plausibly holds that Tay Sachs syndrome (a degenerative disease of the nervous system that commonly causes death before four years of age) is a valuable form of human diversity rather than a horrible disease. Similarly, there are other diseases which have simple genetic mechanisms; and which take decades of life from people (including cystic fibrosis, and spinal muscular atrophy). Such diseases seem likely to be negative rather than neutral forms of genetic diversity.

One option, then, is to limit the use of GGE, to the prevention of severe fatal conditions. Similar principles already govern access to other reproductive technologies like PGD. 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 deemed to be risky can be rejected.

There is no reason why such a system could not work for GGE. A case by case system could work both to reduce rates of fatal genetic disease, and avoid risking traits that may represent valuable types of diversity. If regulated in such a way, GGE could greatly improve the health of future generations

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