Commentary

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Gene editing and the health of future generations

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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 will have on the health of future generations (Note: By 'germline' gene editing, I mean the editing of DNA in cells which could potentially be heritable, e.g. germ cells or embryonic cells.). I argue that provided germline gene editing is well regulated, it could greatly improve the health of our descendants. The use of germline gene editing in research will greatly increase our knowledge of development and could lead to novel treatments for disease. Germline gene editing 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 germline gene editing to prevent disease raises contentious philosophical issues, conceptual uncertainty should not prevent the development of germline gene editing as a research tool and a treatment for fatal genetic conditions.

The research applications of germline gene editing

The most significant question currently facing counties in regards to germline gene editing is whether to use germline gene editing for research purposes. In many countries around the world, such as Canada, Australia and most of Europe, any form of research using germline gene editing 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 of pursuing germline gene editing is very strong.[1] Editing human embryonic stem 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 germline gene editing 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 fertilised embryos survive pregnancy.[3] We have a poor understanding of why this is. Using germline gene editing to study early development could lead to a great understanding of the causes of infertility and to better treatment options.

Germline gene editing can also improve our understanding of genetic diseases. Gene editing allows researchers to generate embryonic system 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 embryonic system 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. Germline gene editing could thus expedite the development of pharmacological therapies for genetic diseases.

While such research can be performed using induced pluripotent stem cells, embryonic system

cells may have technical advantages.[5] Induced pluripotent stem cell models are created from somatic cells, which may have undergone epigenetic changes. As a result, induced pluripotent stem cells may be more diverse and behave less predictably than embryonic system cells in certain applications.

The use of germline gene editing in research, therefore, could improve the health of future generations. By providing a new way to study human development, germline gene editing may lead to better treatments for infertility. Furthermore, germline gene editing 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 germline gene editing in human reproduction. The most obvious clinical use of germline gene editing 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 (preimplantation genetic diagnosis) to reduce the incidence of these conditions, but preimplantation genetic diagnosis is not always effective. When IVF only produces a small number of viable embryos, selection is not possible. Furthermore, preimplantation genetic diagnosis is useless to those who are homozygotes for dominant conditions like Huntington's disease. In these cases, using germline gene editing will be the only way that individuals can avoid serious disease in their children.

Many object that such cases are rare, and that preimplantation genetic diagnosis is effective in the vast majority of cases. But even when selection can be used to avoid disease, germline gene editing may provide the more desirable option. Preimplantation genetic diagnosis involves creating a number of embryos, testing each and then only implanting those most likely to be healthy. Preimplantation genetic diagnosis nearly always results in embryos being discarded. For some, this is an undesirable feature of preimplantation genetic diagnosis, which germline gene editing can avoid. (Note: Such benefits largely depend on germline gene editing developing to the point where it is efficient enough to be used on a single embryo.) Furthermore, the way in which germline gene editing avoids disease may be preferable to preimplantation genetic diagnosis. 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 germline gene editing to avoid disease thus seems more analogous to curing a disease than preimplantation genetic diagnosis.

Furthermore, germline gene editing 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. Preimplantation genetic diagnosis 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 preimplantation genetic diagnosis are likely to be carriers of condition their parents selected against. Germline gene editing 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. Using germline gene editing to prevent single gene disorders will thus provide a more effective way to reduce the incidence of these diseases in future generations than preimplantation genetic diagnosis.

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 germline gene editing 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 germline gene editing could be used to reduce genetic disease. But this raises the question – how far to do we go? Do we use germline gene editing 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 germline gene editing 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 germline gene editing 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, it is 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 germline gene editing.

As noted above, germline gene editing 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 germline gene editing, to the prevention of severe fatal conditions. Similar principles already govern access to other reproductive technologies like preimplantation genetic diagnosis. In the UK, regulations limit preimplantation genetic diagnosis 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 preimplantation genetic diagnosis 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 germline gene editing. 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, germline gene editing could greatly improve the health of future generations

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