Future medicine: Andrew Briggs and Timothy Brears

Ethical considerations in the era of gene synthesis

Synthetic biology is a newly coined term for the design and construction of novel artificial biological pathways, organisms or devices.[1] It generally assumes an element of scale and the application of engineering-like techniques to solve biological problems through a rational process of 'biodesign'.

The success of synthetic biology may help us solve some of the most intractable problems on the planet, from healthcare and agriculture to our over-reliance on petroleum-based products and the environmental damage that results from this. Fundamental to its success will be the ability to synthesise genes at scale and with high accuracy, and to regulate and edit genes to create desired phenotypes. However, as technologies such as gene synthesis and gene editing make ever more progress, inevitable questions concerning how these technologies should be used will arise. This will affect not only how synthetic genes are used in human medicine, but also the use of engineered microbes, plants and domestic animals, where the impact on our environment should be considered. One question to ask is the extent to which existing frameworks are helpful in navigating the issues presented by a potentially radically transformative technology.

Ethics has had an important place in medicine for many centuries. Indeed, the Hippocratic Oath, which traces its history back 2,500 years, instructs physicians to 'help and do no harm'. More recently, Beauchamp and Childress, in *Principles of Biomedical Ethics,*[2] first published in 1979, developed the concept of principlism. Their 'Four Principles' are considered by many to be the standard theoretical framework from which to analyse ethical situations in medicine: (i) *autonomy* – the individual should make his or her own choice; (ii) *beneficence* – act in the best interest of the patient; (iii) *non-maleficence* – do no harm; and (iv) *justice* – apply fairness and equality among individuals. Whereas the principles are not considered absolutes, and conflicts between them may frequently arise, they have the advantage of being broadly acceptable across different cultural, religious and non-religious groups and have provided a powerful guide to medical intervention since their first introduction.

The environmental context

The field of environmental ethics concerns human beings' ethical relationship with the natural environment.The major trigger for the field was the publication, in 1962, of Rachel Carson's *Silent Spring,*[3] which surveyed the negative effect humans have on the environment due to the use of pesticides and their impact on natural ecosystems as well as human health. There is, however, no broad consensus on a framework for how society should consider intervention into the environment, and several ethical approaches have emerged, with varying degrees of anthropocentrism.[4]

The extraordinary progress being made in gene editing and gene synthesis brings into sharp focus what it means to be human,[5] and how to promote human flourishing,[6] because ultimately the specific issues faced on different timescales depend on these bigger questions. There is a strong move in the social sciences away from *Homo economicus* as rational selfish man, seeking to maximise his utility at minimum cost, towards richer concepts such as *Identity Economics*[7] and *What Money Can't Buy*.[8] The scope for an ethical basis to policies and choices is emphasised in *The Future of Capitalism*.[9] Human flourishing can be measured by relatively simple metrics which tend to give results essentially the same as more elaborate methods, by evaluating individuals' self-appraisals of their happiness and life satisfaction, mental and physical health, meaning and purpose, character and virtue, close social relationships, and the financial and material stability necessary to support the other five.[10] Some such measure of human flourishing is necessary in order to evaluate the foreseeable uses of gene synthesis, and hence provide an ethical basis. The most relevant for gene synthesis might seem to be mental and physical health, insofar as these are genetically based, but the issues may prove more subtle.[11]

Whose genes?

The possibility of gene editing to cure certain genetic diseases is already available through CRISPR/Cas9 techniques, and has been approved by the US Food and Drug Administration for trials in the USA. For an individual the ethical basis might seem relatively straightforward against the criterion of improving mental and physical health. If by gene editing (for rare but significant diseases attributable to a single point defect) you can prevent or cure a disability, why not do it? The ethical questions therefore focus on whether the correction should be for that individual only, or for their germline and hence all their progeny.

This issue came to prominence in 2015, sparking global debate, following the publication by Liang *et al.*[12] of the use of CRISPR to correct the mutation leading to muscular dystrophy. This was the first time the human germline had been modified, though the embryos generated, as triploids, were not viable.

The ethical debate on germline editing has many strands. One popular argument is that such an approach is not required as technologies such as *in vitro* fertilisation and pre-implantation genetic diagnosis are already widely used to avoid the transmission of many genetic diseases. But this argument fails to see the huge potential of germline editing to address many more genetic diseases, including polygenic disorders, opportunities that our ever-expanding genetic knowledge and gene synthesis abilities will surely make possible.

More significant, within the ethical context, is the question of safety: how can we be sure that 'off-target' mutations will not cause serious problems for the offspring? How can we reasonably demonstrate that such mutations are likely to be benign? Are they likely to be more or less

significant than the mutations that accumulate during the ordinary course of life and from activities like smoking and drinking and is that, in any case, a fair comparison? Is this about risk/benefit or will we never accept the risk, however small? And finally, who gets to decide on behalf of an embryo that cannot itself provide consent? Assuming a favourable risk/benefit balance, to what extent should this question be decisive in a world where many of our actions already have direct consequences for those who will follow us?

Currently germline editing is not approved, exactly for the reason that a mistake might propagate indefinitely and be impossible to correct. The unforeseen consequences could be of huge magnitude – no one wishes to run the risk of a germ line of genetically engineered thalidomide victims. Indeed, the recent report by Dr He Jiankui of Shenzen's Southern University of Science and Technology of human germline editing, again using CRISPR, was met with universal condemnation across the scientific community as the full consequences of such editing in the offspring could not be known.[13] The ethical issues therefore focus around safety engineering. The level of confidence required needs to be very high, all the more so if it becomes possible to tackle more complex genetically promoted diseases though gene synthesis. If the safety issues could be satisfactorily addressed, there would be everything to be said for curing a disease for a germline in perpetuity. And for this reason, within the established ethical principles of research on embryos, and provided additional controls preventing germline editing are in place, it would be appropriate to allow research on embryos aimed at better understanding the safety consequences of such work.

Curing or enhancing?

Many of the ethical studies draw a sharp distinction between curing, in the sense of restoring healthy bodily function, and enhancing, in the sense of increasing a human capacity in some respect.[14] Such questions are not new; it is notoriously difficult to make a clear distinction between restorative and cosmetic skin surgery. A good way to engage the public in this debate is by analogy with drug enhancement in sport.[15] Have we seen the last Olympic games in which there were no genetically modified athletes? Will the next scandal be not about state-sponsored drug abuse but state-sponsored genetic engineering? How would you detect it? Who would be to blame if the modification were engineered before the athlete was born? Would there be an argument that the subject's autonomy had been undermined? Having caught the public imagination in that way, one then needs to recognise that sport consists of voluntarily accepting arbitrary rules, and that there are more serious issues. It is arguable that community health care interventions, such as avoiding water contaminated by cholera and vaccinating against smallpox and other preventable diseases, make as great a contribution to human health as all the hospitals in the world. If then we are glad that poliomyelitis can be prevented by vaccination, what if incidences of other diseases can be reduced or eliminated by gene synthesis. Suppose that a given genetic modification would significantly reduce the risk of a painful and fatal cancer. Should you do it? If so, should that be restricted to individuals who can afford to choose it and pay for it, or should it be available to the population as a whole?

What about the environment?

One of the most significant questions in recent years has been the release of genetically modified (GM) plants into the environment. This raises a variety of issues from safety, to biodiversity and the more opaque question of the extent to which GM should not be permitted as it is 'unnatural.'

A central question has been that of safety – is it safe to eat GM plants and is it therefore ethical to allow GM plant material into the food chain where individuals who may not choose to do so are exposed to the risk? Clearly data can be used to address the question of safety, as it can for a new drug, and regulatory agencies have sought to address the question of involuntary exposure by requiring the labelling of GM produce. The overwhelming consensus to date is that GM food provides little or no safety risk, nor is it of lower nutritional value than conventional food.

A second question concerns the potential risk to biodiversity from the use of GM crops and the unintended 'escape' of genes, by pollen transfer, into wild plants, which may then be selected for, propagate, and change the character of the environment. Again, this has largely been addressed through the regulatory framework, but answers can usually only be found on a case-by-case basis.

In addition, many contend that a GM plant (or no doubt a microbe) is 'unnatural' as it may contain a gene from another species. This, coupled with the possibility of horizontal gene transfer, presents a barrier to the acceptability of the technology by some, regardless of the potential benefit. This raises the question: how dominant should 'benefit' be in the ethical debate? The principles of Beauchamp and Childress would say 'yes' provided it is viewed together with the other principles.

It is apparent that there are clear benefits from some transgenic crops, not only to the farmer but also the consumer. Most notable among these is 'Golden Rice' (still in development), which provides a source of vitamin A, deficiency of which can result in children dying of common infections and suffering irreversible blindness.

In such cases where our perception is that the risk/benefit is heavily weighted in favour of the benefit, perhaps the question to ask is: is it ethical *not* to allow the development of GM crops with the potential to alleviate such misery in the world? Given an adequate regulatory framework, what are the risks that would preclude us from developing such a product?

Are we at risk of playing God?

A question that often arises is: will the new technology provide scientists with a level of omnipotence that is inappropriate or should make us feel uncomfortable? To the extent that DNA and genes exist in many forms, creating a huge variety of organisms, each reflecting a different point along an evolutionary pathway and timescale, should we see our interventions as providing a helping hand in an evolutionary process? In the Anthropocene era humans have already achieved unprecedented control over this creation, and the responsibility which comes with that extends to the processes of evolution. Since the invention

of farming, humans have directed evolution through selective breeding of crops and domestic animals with significant consequences for human flourishing. But the deployment of gene synthesis to accelerate or re-direct evolution provides an increasing burden on us to determine the purpose of evolution and do so within the context of our greater responsibility for the planet and its resources. The application of gene synthesis to humans depends on questions which may be even more profound, all the more so if it may impact generations not yet born. We should not be afraid of such questions, but we should proceed cautiously while we address them and apply the answers to practical possibilities.

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Further resources – reports on the ethical issues associated with the science of gene synthesis

Genome Editing: an ethical review. Nuffield Council on Bioethics (2016)

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This article was written by Andrew Briggs, a member of the Scientific Advisory Board of Evonetix Ltd, and Timothy Brears, the company's chief executive.

