Progress Educational Trust
informing debate on assisted conception and genetics

Genome Editing
Open Call for Evidence by the Nuffield Council on Bioethics

Response by the Progress Educational Trust
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*The **Nuffield Council**'s Call for Evidence groups questions into six sections. We have responded only to questions in the two sections that are most relevant to our charity's remit – '**Perspectives on Genome Modification**' and '**Biomedical Research and Human Applications**'.*

I) PERSPECTIVES ON GENOME MODIFICATION

- **Is there anything special about the genome that makes intervening in it different from other ways of manipulating nature (eg, selective breeding of plants or animals)?**

  Broadly speaking, no. The fact that we are in a position to consider intervening purposefully in nature at such a fundamental level as the genome speaks to remarkable scientific advances, but is ultimately still a part of humanity's ongoing trajectory of investigating and manipulating nature to human advantage. In future, we may develop interventions in nature that are more intricate still.

  It is also worth remembering that even intervention in nature often draws upon nature, rather than representing a completely alien incursion into the natural domain. The CRISPR approach to genome editing was not invented in complete isolation from the natural world and then introduced into it, but rather was adapted from a naturally occurring mechanism used by bacteria as a defence against invading viruses.

- **To what extent can the development of genome editing techniques be regarded as distinct from or continuous with existing techniques? In what way are the differences significant?**

  The development of genome editing techniques is very much a logical part of, rather than being distinct from, the development of other techniques of investigating and manipulating genes. The history of genome editing – successive breakthroughs, over the course of three decades, in the development of targeted gene insertions and knockouts and in the use of various guide molecules and (endo)nucleases to edit gene sequences – cannot be disentangled from wider advances and developments in biomedicine.

  If genome editing sometimes appears to represent a radical break with the past, this is due largely to the rapid increases in its accuracy and efficiency – and decreases in its cost and difficulty – brought about by CRISPR, which is proving to be something of a disruptive technology. If CRISPR appears to have become suddenly ubiquitous, imbuing bioethical discussion with a sense of urgency, this state of affairs is the result of developments that can be traced back decades (notwithstanding the fact that the rapid culmination of these developments has caught many people and organisations on the back foot).

With the advances brought about by CRISPR, the range of possible varieties and applications of genome editing is now so wide that distinctions within the field – between somatic and germline, between research and therapy, and between human, animal, plant and microbe – are arguably just as significant as distinctions between genome editing and other areas of biomedicine, if not more so.

- **What obligations do scientists involved in developing and using genome editing technologies owe to society and what freedoms should society allow to these scientists? Do genome scientists have any special obligations to society that are distinct from those of other scientists?**

  One of the key obligations that scientists working in this field owe to society is the obligation to explore the potential of genome editing as thoroughly as possible, within the parameters of current regulation. Genetic conditions in particular are not always well understood, and tend to lack effective treatments. Genome scientists should be seeking to improve this situation.

  Society, in turn, has an obligation to the scientists – an obligation not to impede their work where the work is lawful, to help with the funding of their work (either by providing public funding or by encouraging private funding), and to understand and help to promulgate their work (by improving the public understanding of science, and by raising the level of ethical and political debate).

  Genome editing scientists do not have any special obligations distinct from those of other scientists, except inasmuch as their field can be especially challenging for the layperson to understand. ZFNs, TALENs and CRISPR come atop an already high mountain of genetics-related acronyms and jargon, describing processes which can have a major impact on people's lives.

  Scientists need to lighten the burden of comprehension where possible, by explaining their work clearly and engagingly and by fielding questions and criticisms from outside their profession.

- **To what extent is the development of genome editing valuable as a pure research tool, and to what extent is its value dependent on envisaged practical applications?**

  Genome editing is extremely valuable as a pure research tool, giving us the ability to ask and answer questions about some of the most fundamental aspects of biology. The ability to conduct unprecedentedly precise and intricate experiments at the molecular level is a game changer, and could add immensely to the sum total of human knowledge. This new knowledge cannot help but bring to our attention new practical possibilities – possibilities which may or may not involve further application of genome editing.

  It is important to remember that research using genome editing can yield insights which have practical applications elsewhere. Take the UK's first licensed human embryo research using CRISPR, led by Dr Kathy Niakan at the Francis Crick Institute, which is investigating the genes involved in the first seven days of embryo development. Such research could ultimately lead to improvements in assisted conception techniques, or at the very least an improved understanding (beyond trial and error) of how and why such techniques work, without the techniques themselves necessarily involving any genome editing at all.

  The value of genome editing as a pure research tool is not contingent upon its practical applications. Speculation about envisaged practical applications is useful (not to mention exciting!) and has its place, but should not be used as a pretext to restrict pure research.

Practical applications do not have to follow ineluctably from pure research. Rather, pure research leaves us better placed make a well-informed decision about whether or not a specific practical application should be investigated.

- **What obligations do governments have towards society to ensure 'safe' science or otherwise to shape the scientific research and development?**

  It is incumbent upon governments and legislators to regulate scientific research and practice, either directly or via specialist regulators, to ensure that well-defined and proportionate standards of safety are met. This applies to genome editing just as it applies to any field of scientific endeavour involving some degree of risk (risk is inevitable, especially in therapeutics).

  A narrative is forming around genome editing which suggests that somatic applications of the technology are safer and will be developed first, whereas germline applications of the technology are riskier and will take longer to satisfy the requisite safety standards. There is some truth to this, but it is a position that may change.

  For example, editing the genome of a single-celled gamete or embryo may transpire to be considerably safer than editing millions of cells (as typically occurs in somatic cell therapies), because there will be a lower risk of accidental modifications to the gene sequence and a lower risk of mosaicism.

- **What conventional moral principles, if any, do genome editing challenge?**

  Genome editing does not pose a particular challenge to conventional moral principles. Those whose principles leave them well-disposed towards humans intervening in nature to improve their lot will feel less challenged by genome editing than those whose principles leave them ill-disposed towards humans intervening in nature.

  This disposition will in turn shape perceptions of the technology's possible benefits and risks. When lauding or damning the technology, it is important to try to distinguish between arguments that rest on scientific grounds and arguments that rest on moral grounds (even though these two domains cannot be completely decoupled, science being a moral endeavour in many people's view).

  The use of genome editing to modify early human embryos for research purposes, without any intention of establishing a pregnancy, fits comfortably under the auspices of the moral principles that apply to all embryo research. This fact is well reflected in UK legislation, where the relevant regulator (the HFEA) is already empowered by statute to grant licences for such research on early human embryos, and indeed has already done so (licensing Dr Kathy Niakan's research at the Francis Crick Institute).

  The prospect that we may in future edit the genomes of gametes or embryos, to ensure or to prevent the presence of selected characteristics in a child, has provoked the same expressivist concern as earlier reproductive technologies – the concern that use of the technology will encourage stigmatisation of, or prejudice against, people with disabilities or with other deprecated characteristics. A related criticism is that by proactively choosing one possible future child over another, prospective parents commit the morally abhorrent act of negating the life of the child who was not chosen.

We do not agree with these perspectives. We believe that having the latitude to choose between hypothetical future people is innocuous, and is not tantamount to impugning or ending the existence of an actually existing person (which would indeed be morally abhorrent).

We also believe that the best way to assuage expressivist concerns is to enter into open and honest discussion with those who harbour such concerns, rather than seeking to restrict the choices available to prospective parents.

- **To what extent can the moral questions raised by genome editing be addressed using existing moral frameworks or approaches?**

  The UK has a well-established set of approaches and institutions for considering moral questions in biomedicine (including exercises such as the very consultation to which we are responding), and there is no reason to doubt the adequacy of these approaches in addressing the moral questions raised by genome editing.

  One possibility raised by genome editing, which some people find morally challenging and which the UK is particularly well placed to address, is the possibility of changing the human germline – of making changes in the course of assisted conception which will affect not only the child born, but also subsequent generations.

  Both assisted conception and its regulation are fields that were pioneered in the UK, with the first IVF baby born in the UK in 1978 and with the Warnock Report of 1984 leading to the establishment of the HFEA in 1990. Until IVF babies grew up and started having babies of their own – including Louise Brown's son, who was conceived naturally only a decade ago – the impact of IVF on successive generations was necessarily a matter of some uncertainty.

  Now that the UK is the first country to legislate for the use of an IVF technique that purposefully changes the germline (mitochondrial donation), the country's clinicians and regulators are leading the way in devising appropriate protocols for clinical follow-up and longer-term research.

- **To what extent are laws and legal frameworks necessary or desirable in seeking to ensure adherence to the moral principles that should inform genome editing?**

  Laws, even if they are drafted with moral principles in mind, do not actually ensure adherence to moral principles. Rather, they provide clarity by defining what it is and is not legally permissible to do in a given jurisdiction. Whether or not it is *morally* permissible to do something is a question on which there is far greater scope for legitimate differences of opinion.

  By establishing clearly what is and is not permissible, legal frameworks promote confidence on the part of both people working within a particular framework (in this case researchers and clinicians) and people looking on from outside (the general public and people in other jurisdictions).

  Legal frameworks lend coherence and transparency to scientific developments, and to the way the public relates to such developments. By contrast, in a poorly regulated environment, work that pushes back the frontiers of what is knowable and what is doable can seem disconcertingly haphazard and opaque. We have a responsibility to ensure that genome editing is developed in the former environment, rather than being left to the latter.

- **What other issues do you feel need to be discussed in the context of genome editing? What do you consider to be the issues of greatest moral concern raised by genome editing?**

We think it is important to discuss the distinction (or rather lack of one) between therapy and human enhancement. 'Human enhancement' is often discussed as though it is self-evidently a step beyond therapy and more frivolous than therapy, but this is misleading.

All manner of improvements to human health can be considered enhancements, especially when they have the cumulative effect of steadily increasing average human longevity. Vaccinations conferring immunity to disease are a good example of enhancement. Unlike the difference between somatic and germline applications to genome editing, where a clear and important distinction can be made, we are not persuaded that there can always be a meaningful distinction between therapy and enhancement.

We are reassured by the fact that with or without an edited genome, children will – by virtue of being human – continue to grow into autonomous people whose personality is unforeseeable, and whose destiny is in their own hands.

II) BIOMEDICAL RESEARCH AND HUMAN APPLICATIONS

- **What is the current state of the art in the field? what are the current technical limitations and constraints/bottlenecks?**

Many of the technical limitations that previously restricted genome editing have been lifted by the advent of CRISPR, with its improvements in accuracy and efficiency.

A challenge that remains is the problem of accidental rather than intended modifications to DNA. These 'effects' or 'events' can be 'off-target' (occurring in parts of the sequence that that were *not* targeted with an intended modification), and can also be 'on-target' (occurring in parts of the sequence that that *were* targeted).

Looking for these accidental modifications is no simple matter – it involves sequencing whole genomes before and after genome editing has taken place, in order to make comparisons. Then there is the added challenge of distinguishing these accidental modifications from discrepancies between genomes due to naturally occurring somatic mutations (mutations whose frequency in our cells increases as we age).

Whether the aim is to edit the genomes of many cells, or whether the aim is to edit the genome of one cell or a few cells (a gamete or embryo) which will in turn give rise to many cells, there is the challenge of mosaicism – unintended genetic variation between cells. Where genome editing experiments are carried out on human embryos, mosaicism is less likely if the genome is edited at an earlier stage of embryo development.

The upshot of this is that while it is useful to carry out research on nonviable embryos donated by fertility patients – for example the pioneering Chinese research which used CRISPR on human embryos in 2015, see http://dx.doi.org/10.1007/s13238-015-0153-5 – it will be even more useful, in the longer term, to create human embryos specifically for research and subsequent destruction.

Indeed, as the Hinxton Group argues – see http://bit.ly/1j9WT6A – doing this will be necessary if experiments in this area are to make progress.

Efforts to detect and minimise accidental modifications and mosaicism, and understand the consequences of these phenomena, are important and ongoing.

- **What are the main directions of travel? what are the envisaged endpoints/applications?**

  The main directions of travel in biomedical and human applications of genome editing are research improving our understanding of human biology (including genetic disease), the development of somatic cell therapies, and – looking further ahead, and provided that various conditions are satisfied – increasing the reproductive options available to people (including carriers of genetic disease) who wish to give birth to a healthy child.

  Looking even further ahead, if we are ever in a position to derive gametes *in vitro* (creating viable human germ cells by inducing pluripotency in somatic cells), then genome editing tools could also play an important part in that process. However, this is still a distant prospect, legally as well as scientifically. A change in law would be required in the UK before it was permissible to use *in vitro* derived gametes in treatment, regardless of whether or not genome editing was involved.

- **What are the main 'drivers' and 'obstacles' in relation to envisaged endpoints?**

  Commercial interests are important in driving developments in genome editing. A report by the market research company Markets and Markets – see http://bit.ly/23o5ipN – estimates that the genome editing industry will be worth $3.5 billion by 2019. This industrial growth will help expedite the achievement of envisaged endpoints, but also underlines the importance of policymakers, regulators and non-commercial actors exerting some influence in the field.

  The CRISPR approach to genome editing is currently the subject of a high-profile intellectual property dispute in the USA, the resolution of which has the potential either to impede or to assist in the development of genome editing. Whether advances in genome editing are on balance helped or hindered depends on how long it takes for the dispute to be resolved, and how the prevailing patent holders choose to use and enforce their patent rights.

- **What bearing do international ethical debates and agreements (eg, high level statements or calls for moratoria) have on the pace or organisation of research?**

  International ethical debates and agreements have a significant impact on research. Overly restrictive or insufficiently clear regulation, or the prospect of such, can act as a serious disincentive to public and private funding.

  One of the most important challenges in debates and agreements concerning genome editing is to retain a clear sense of the distinctions between the many different possible applications of this technology, so that these applications can be given specific and separate consideration. It should be possible for national and international institutions to calibrate their approach to genome editing, so that some applications of the technology are approved even if others are not, and so that basic research can proceed.

It is also important for debates and agreements to take account of developments as they unfold, in what can be a very fast-moving area. As the Hinxton Group argues – see http://bit.ly/1j9WT6A – *'policies governing science nationally and internationally ought to be flexible, so as to accommodate the rapidity of scientific advance as well as changes of social values'*.

Moratoria are profoundly unhelpful in relation to genome editing. They are unnecessary in well-regulated jurisdictions, they are ineffective in poorly regulated jurisdictions, and they are liable to be blunter and less granular than *de jure* regulation with the result that diverse applications of genome editing are all tarred with the same brush.

Unless the terms of a moratorium include clear deadlines and mechanisms for review, then a moratorium amounts to an indefinite and disingenuous ban. In the absence of clear sanctions for breaching the terms of the moratorium, the harshest consequence for such a breach is liable to be the prospect of bad publicity – a prospect that brasher organisations will take in their stride, allowing them to steal a march on more scrupulous organisations who will find themselves struggling for approval and funding. The net result of a moratorium is likely to be apprehension and confusion, when what is really required in this area is confidence and clarity.

As our director Sarah Norcross argued in the *Observer* in 2015 – see http://bit.ly/1PTfYE9 – *'We think a debate about any new scientific advance is informed and enriched by continued research to understand and refine these techniques in a laboratory, under strict regulatory limits and scientific scrutiny. Many of the questions that the public and policymakers will rightly raise can be answered only if researchers are actively investigating the techniques, testing a variety of hypotheses and advancing their own knowledge. A moratorium on research would be a moratorium on this understanding.'*

- **Who should lead and who should be involved in setting policy for research and human applications of genome editing? is this significantly different from other kinds of experimental or reproductive medicine?**

The protagonists of genome editing – the researchers, policymakers, regulators and critics – are not substantially different from the protagonists of any other area of experimental or reproductive medicine. We do not believe there is a need to establish a new policy or regulatory body to lead on this subject in the UK at the present time.

Of course, it is vital for the general public to be involved in discussion of any experimental or reproductive medicine that breaks new ground and stands to have a major impact on society. This is certainly the case in relation to genome editing.

As well as the lay public learning from experts, we must also remember that the lay public is more than capable of coming up with useful and counterintuitive ideas that make experts see biotechnology with fresh eyes. Our own charity specialises in organising events where experts and laypeople learn from one another, and we can testify to the fact that this approach is invaluable.

Even the most outlandish suggestions and thought experiments by ethicists, philosophers, science fiction authors and members of the public have a role to play, in ensuring that we think in an open-ended way about groundbreaking technologies such as genome editing. That said, we must always take great care to distinguish between fact and fiction, and to distinguish between what is currently or imminently possible and what is more speculative.

- **What are the significant decisions that need to be taken before therapeutic use of genome editing may be contemplated (for non-heritable and heritable genetic changes) and who should have the responsibility for those decisions?**

  The distinction between somatic and germline therapy is especially important here. Genome editing is already having a significant impact on somatic gene therapy, a field that that has existed for decades but has faced formidable challenges and setbacks, meaning that it has been slow to move beyond the experimental phase.

  Genome editing provides a means to circumvent some of these obstacles and has already yielded some remarkable results, such as the use of TALENs to reverse advanced leukaemia in one-year-old British baby Layla Richards in 2015. Such experimental therapies are subject to well-established standards of safety, ethical scrutiny and clinical judgement, and are legally permitted in the UK if they meet these standards.

  The use of genome editing in germline therapy, by contrast, would not be possible in the UK without a change in the law. And for good reason.

  The **Nuffield Council** argued persuasively in a 2012 report – see http://bit.ly/1K8Q515 – that mitochondrial donation techniques used in treatment should be regarded as germline therapies. Following the passing of Regulations by Parliament in 2015, two such therapies can now legally be used in the UK, if a licence is granted by the HFEA. The reason these germline therapies are currently permitted, while other germline therapies would not be permitted, is not because the law is capricious but rather is because of an important distinction.

  Mitochondrial donation is a special case where the germline is changed by moving DNA molecules from one place to another *without* changing the gene sequence within these molecules. Genome editing, by contrast, *does* involve changes to the gene sequence, thereby offering different possibilities and involving different risks. It is reasonable that if there is case for permitting germline genome editing in therapy, then this case needs to be made anew and the law changed accordingly.

  Parliament is responsible for deciding whether or not to change the law. Before it can do so, it will need to be satisfied that the relevant genome editing techniques are safe and efficacious (to the extent that this can be established in non-human models and early embryos), and it will need to consider the specific use(s) to which the techniques might be put. Crucially, the public's opinion on the matter will need to be sought and assessed.

  The past decade of UK deliberation on the subject of mitochondrial donation has involved a flexible yet robust strategy, which has allowed scientists and policymakers to keep abreast of one another. Lessons learned from this experience will be useful when it comes to genome editing and the law.

- **Are the benefits and costs of treatments that involve genome editing likely to be distributed equitably (or any more or less equitably than existing or alternative treatments)? In what way might genome editing differentially affect the interests of people in vulnerable or marginalised groups?**

  It is difficult to answer this question in the abstract, as the answer would depend very much on the specific treatment. In the UK, the answer would also depend on whether and how the NHS

commissioned the treatment – central commissioning by the NHS is very different from local commissioning by CCGs, with the latter liable to result in inequity.

Speaking more generally, it is usually a safe bet that the affluent will be able to avail themselves – to a greater or lesser extent – of treatments that others will find more difficult to access. This is true of all medicine, and is perhaps especially true of reproductive medicine.

If whole genome sequencing becomes more routine, then subclinical or ambiguously pathogenic gene variants may come to light via sequencing, which might never have affected a person's health. Some may seek to improve their health – or, regulation permitting, the health of their offspring – by modifying the relevant genes with genome editing. Some may be able to afford to do this, while others may not.

This hypothetical scenario poses some challenges, but it is not entirely new. As with all of health, treatments of questionable value may be offered alongside treatments that are of obvious value (to the extent that this is possible within the terms of regulation), and the former may be commercially driven and may promote or exploit unnecessary anxiety. Education and public engagement, to put risks and benefits in context and to encourage enlightened scepticism, will be important to mitigate this.

Some have expressed concern that the vulnerable or marginalised will experience greater stigma and discrimination as a consequence of genome editing. This is a form of the expressivist objection to reproductive choices – as we have explained above, we do not think this objection is well-founded. Nor do we agree with fears that genome editing will bring about a resurgence of eugenic thinking.

Eugenics, when it pervaded mainstream thought in the nineteenth and early twentieth centuries, was predicated on the belief that people were divisible into racial types – some of which were considered superior, while others were supposedly subhuman. This belief has been thoroughly discredited, both scientifically (by advances in our understanding of genetics) and politically.

Eugenics involved a singular mythical ideal of human inheritance and perfection, manifest in the concept of race and in the idea of perfect or perfectible (eu)genes. Eugenicists also argued for coercive means of achieving this mythical ideal.

There is currently no widespread belief in or appetite for such a singular idea of human perfectibility on racial or other such spurious grounds, and there is no credible suggestion that people should be coerced into particular reproductive outcomes. Furthermore, our understanding of genes is now far more sophisticated.

In short, genome editing will not revive a eugenic outlook.