

This response was submitted to the Call for Evidence held by the Nuffield Council on Bioethics on *Genome editing* between 27 November 2015 and 1 February 2016. The views expressed are solely those of the respondent(s) and not those of the Council.

## ***Nuffield Council on Bioethics***

### **Genome Editing**

#### **Submission from the Christian Medical Fellowship (CMF)**

*'The Council is inviting written submissions of evidence to inform its examination of ethical issues arising in relation to genome editing, an emerging family of biological techniques for making precise genetic alterations to living cells.'*

<http://nuffieldbioethics.org/project/genome-editing/open-call-for-evidence/>

The Christian Medical Fellowship (CMF) was founded in 1949 and is an interdenominational organisation with over 4,500 British doctor members in all branches of medicine, and around 800 medical student members. We are the UK's largest faith-based group of health professionals. A registered charity, we are linked to about 80 similar national bodies in other countries throughout the world.

In this submission, CMF offers comments on a number of the issues and perspectives that the Council has proposed for discussion.

### **1. Perspectives on genome modification**

#### **1.1 The distinctive significance of genome interventions**

Genome-editing technologies (such as ZFNs, TALENS and CRISPR) currently appear to offer novel and powerful approaches to modify genomic sequences and treat many human diseases, including HIV/AIDS, haemophilia,<sup>1</sup> sickle cell anaemia and several forms of cancer.<sup>2</sup>

The newest of these technologies, CRISPR, is just three years old but already thousands of labs are doing important research using it. Research that used to take many years and that was very costly is now quicker, more efficient and vastly cheaper.

The examples of Layla Richards<sup>3</sup> last year, of trials of therapies using TALENS on people with HIV in the US<sup>4</sup> and of potential 'cures' for inherited retinitis pigmentosa, are just three

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<sup>1</sup> <http://www.engadget.com/2015/12/03/worlds-first-in-human-CRISPR-hemophilia/>

<sup>2</sup> 'Zinc-finger nucleases (ZFNs), transcription activator–like effector nucleases (TALENs), and CRISPR/Cas RNA-guided nucleases (RGNs)...As a group, these reagents have been successfully used to modify genomic sequences in a wide variety of cells and organisms, including humans'.

<http://www.annualreviews.org/doi/abs/10.1146/annurev-biochem-060713-035418>

<sup>3</sup> <https://www.newscientist.com/article/dn28454-gene-editing-saves-life-of-girl-dying-from-leukaemia-in-world-first/>

<sup>4</sup> <https://www.newscientist.com/article/mg22630194-200-human-gene-editing-has-arrived-heres-why-it-matters/>

examples of the remarkable and exciting progress being made.<sup>5</sup> All techniques currently in various stages of clinical development focus on modifying the genetic material of **somatic cells**, such as T cells. These are not designed to affect sperm or eggs.

The current research and proposals are very broad and, despite the media hype, are not primarily about germline engineering or modifying embryos but are about working with somatic cells.

**This distinction, between genome editing in somatic cells and in germ cells, is crucial.**

**We, along with many others, have grave concerns about the safety and ethical impact of germline editing (see later) and failing to distinguish between germline and somatic cell editing may well impede the significant progress being made in the clinical development of ethical approaches to cure potentially serious debilitating diseases.**

Many scientists working on gene therapy and regenerative medicine are concerned that risky attempts to change the genetic inheritance of our species may well provoke a backlash (in the UK, EU and elsewhere) against important scientific efforts to treat disease in people who are suffering today.

**We welcome and support beneficial and ethical applications of genome editing on somatic cells, but we strongly oppose those that modify germ cells.**

Moreover, at such an early stage, it is important to keep expectations of genome editing under control, free from hype and the playing down of risks.

## **1.2 What obligations do scientists involved in developing and using genome editing technologies owe to society and what freedoms should society allow to these scientists?**

These are not simply scientific questions, they are issues of philosophy, ethics, governance, social acceptance and media influence.

Scientists are responsible for working within legal and ethical boundaries. They have no more right to decide these boundaries than any other member of the public. Scientists do not always like self-regulation<sup>6</sup> but they have a public duty and responsibility fully to inform the public about the risks, realistic benefits, purposes and any vested interests in their research, in order to build public trust in responsible science. They have an obligation to be realistic regarding safety evaluations, possible (irreversible) outcomes and time scales, and not prematurely to hype possible benefits. Scientists are responsible for keeping expectations of genome editing tools under control.

This is particularly so with morally controversial research but it has not always been the case.

Note, for example, much of the premature hype around creating animal-human hybrids which, years after Parliament permitted them, has not lead to any therapies or investment,

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<sup>5</sup> 'Cure' for inherited blindness gives hope. The Times 28 January 2016.

<sup>6</sup> <https://www.youtube.com/watch?v=y7LXwGfxxwo>

despite the promises that it would save millions of people!<sup>7</sup>

The UK is in a unique position in genome interventions in that we have legalised the genetic modification of human embryos for mitochondrial disorders. While this is currently tightly regulated, it has introduced both public and legal *acceptability* of genetic modification of human embryos for the first time. Although this use of this technology will be limited, (to only a few women), it has served to foster a climate of increasing acceptance of human genetic modification, making both the public *and* scientists more comfortable with genetic modification in principle. We strongly caution against prematurely creating an ever more acceptable environment in the UK for human genetic modification.

Scientists should prioritise research on *alternatives* to ethically controversial work. Human germline modification is presented as a way in which to prevent transmission of inherited diseases but in most cases couples at risk of passing on genetic diseases can use alternatives - prenatal screening, pre-implantation diagnosis, adoption or donated gametes - to have healthy and genetically related children, without manipulating genes. Several of these alternative options are ethically controversial but are generally safe, effective and offer a more realistic alternative to germline editing for couples. And of course, germline editing would still involve use of IVF and screening. Francis Collins, Head of the NIH, has made it clear that editing the germline is unethical, unsafe and unnecessary and there are suitable alternatives.<sup>8</sup>

Moreover, as we note below, UK scientists ought to be responsible for working within both national and international laws and regulations.

### **1.3 Do genome scientists have any special obligations to society that are distinct from those of other scientists?**

Yes. Despite the hype and enthusiasm, this is a very new technology and there is widespread concern about both the ethics and safety of germline genome modifications, because of its impact on future generations, its potential for unintended and off-target harm, its irreversibility, its hard-to-calculate long-term consequences and because of the research needed on embryos. This all requires high levels of trust in scientists to remain within national and international safety and ethical guidelines.

Genome scientists are working with particularly powerful tools that have the potential for new research and therapies, research that used to take years and cost millions but that is now far quicker and cheaper.

However, these techniques are also able to open the way to scientists who wish to push legal and/or ethical boundaries, driven by ideology and/or the chase for profit, and who simply ignore international agreements.

Despite early public calls for CRISPR/Cas9 research to be halted, a Chinese research group has already attempted to genetically modify human embryos.<sup>9</sup> The treatment killed nearly one in five embryos and only half of the surviving cells had their DNA modified. Of the cells that were even modified, only a fraction had the disease mutation repaired. The study also

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<sup>7</sup> <http://www.theguardian.com/commentisfree/2008/may/18/stemcells.medicalresearch>

<sup>8</sup> <https://thedianerehmsow.org/audio/#/shows/2016-01-05/gene-editing-the-possibilities-and-risks/111721/@00:00>

<sup>9</sup> <http://www.nature.com/news/chinese-scientists-genetically-modify-human-embryos-1.17378>

revealed off-target DNA cutting and incomplete editing among all the cells of a single embryo.

Yet the general public remains in the dark about the significance and outcome of this crossing of a germline in creating, for the first time, genetically modified human beings, and instead primarily hear the enthusiasm around the many anticipated benefits - which may or may not be justified.

With a technology that is so new - just three years old - it is too premature to know about unintended consequences and we would urge far more caution. As we note above, the UK has already engendered an acceptance of the general principle of germline genetic modification, and we urge great caution in extending this acceptability in anyway.

Several scientists have warned on genomic editing in the Journal *Nature* that: '*we cannot image a situation in which its use in human embryos would offer a therapeutic benefit over existing and developing methods.*'<sup>10</sup>

We therefore support international calls for a voluntary moratorium among genome scientists for human germline modification, including on human embryos. Calls for a voluntary moratorium have mostly been widely welcomed, except from the UK.

**This would not harm all genome research but would focus it onto somatic genetic editing.**

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

Governments are obligated to ensure the safety and well-being of their citizens. This includes protection from the use of harmful research, as well as encouraging the development of therapies to treat and heal. Hence we support calls for a moratorium on germline research (see above).

Governments should also take responsibility for restricting the development of **genetic tourism**. We already see medical and fertility tourism today (eg. with the use of surrogates abroad) and were the UK to step further out of line with other European countries we would create a complex global picture with a possible moratorium in Europe, but not in the UK. Each country needs to enter into a wider discussion to reach consensus internationally of what is acceptable and what is too risky. At the moment, the UK is more isolated than other countries in this respect.

#### **International obligations**

The protection of the health and well-being of all citizens is not solely the responsibility of national government, but also of international bodies. To undermine the widespread policy agreements among many democratic nations is a serious issue. Many other countries and scientists refuse to even countenance germline editing: more than 40 countries and several international bodies including the Council of Europe prohibit genetic alterations that extend to future generations.

When it comes to manipulation of the human germline, governments ought to look for

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<sup>10</sup> <http://www.nature.com/news/don-t-edit-the-human-germ-line-1.17111>

guidance to international bodies, such as the UNESCO Universal Declaration on the Human Genome and Human Rights.<sup>11</sup> Article 24 states that germ-line interventions 'could be considered as a practice' that would be 'contrary to human dignity'.<sup>12</sup>

The International Bioethics Committee of the UNESCO recently published a report on Germline Gene Therapy with a re-emphasis that: *'interventions on the human genome should be admitted only for preventive, diagnostic or therapeutic reasons and without enacting modifications for descendants, as affirmed in Article 13 of the Oviedo Convention. The alternative would be to jeopardize the inherent and therefore equal dignity of all human beings and renew eugenics, disguised as the fulfilment of the wish for a better, improved life.'*<sup>13</sup>

The Council of Europe's Convention on Human Rights and Biomedicine, Article 13 states that *'an intervention seeking to modify the human genome may only be undertaken...if its aim is not to introduce any modification in the genome of any descendants.'*<sup>14</sup>

The EU Charter of Fundamental Rights Article 3 (2) states that: *'In the fields of medicine and biology...the prohibition of eugenic practices, in particular those aiming at the selection of persons'* must be respected.

The approach currently being advanced by a few scientists in the UK<sup>15</sup> contrasts with the firmer line taken by researchers and Government in the US. Significantly, Francis Collins, Director of the NIH, has strongly stated opposition to germline editing in human embryos:

*'NIH will not fund any use of gene-editing technologies in human embryos. The concept of altering the human germline in embryos for clinical purposes has been debated over many years from many different perspectives, and has been viewed almost universally as a line that should not be crossed. Advances in technology have given us an elegant new way of carrying out genome editing, but the strong arguments against engaging in this activity remain. These include the serious and unquantifiable safety issues, ethical issues presented by altering the germline in a way that affects the next generation without their consent, and a current lack of compelling medical applications justifying the use of CRISPR/Cas9 in embryos.'*<sup>16</sup>

## **UK Regulatory Bodies**

We are concerned about the responsibility given to the HFEA both to adjudicate on the use of germline editing in embryos and to oversee the research itself.

Comments recently made by Sir James Munby, President of the Family Division are revealing and concerning: *'The creation, storage and implantation of human embryos is controlled and regulated by the complex provisions of the Human Fertilisation and Embryology Act 1990...The picture revealed is one of what I do not shrink from describing as widespread incompetence across the sector on a scale which must raise questions as to the adequacy if*

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<sup>11</sup> [http://portal.unesco.org/en/ev.php-URL\\_ID=13177&URL\\_DO=DO\\_TOPIC&URL\\_SECTION=201.html](http://portal.unesco.org/en/ev.php-URL_ID=13177&URL_DO=DO_TOPIC&URL_SECTION=201.html)

<sup>12</sup> <http://unesdoc.unesco.org/images/0023/002332/233258E.pdf>

<sup>13</sup> Press Release: <http://en.unesco.org/news/unesco-panel-experts-calls-ban-editing-human-dna-avoid-unethical-tampering-hereditary-traits>

<sup>14</sup> <http://www.coe.int/en/web/conventions/full-list/-/conventions/treaty/164>

<sup>15</sup> <http://www.bbc.co.uk/news/health-35301238>

<sup>16</sup> <http://www.nih.gov/about-nih/who-we-are/nih-director/statements/statement-nih-funding-research-using-gene-editing-technologies-human-embryos>

not of the HFEA's regulation then of the extent of its regulatory powers.<sup>17</sup>

## **1.5 What conventional moral principles, if any, does genome editing challenge?**

Again, there needs to be a distinction made between different types of genome editing. We focus here on the moral concerns with *germline* genome editing.

### **i. Safety**

One of the immediate ethical issues is practical. Patient safety is generally the paramount concern amongst scientists: *'Germline modification has well-recognised safety concerns and the on-going instance of off-target mutations in genome editing means that safety should continue to be considered.'*<sup>18</sup>

As well as cutting the intended DNA, CRISPR/Cas9 often finds unintended targets elsewhere and, just as with its predecessors, ZFNs and TALENS, it can cut the DNA in the wrong spot.<sup>19</sup> Even being off by one nucleotide can cause great harm to an organism. In the laboratory that may not matter but in people it would clearly matter. This technology is only three years old so it is still far too early to know about its impact on future generations, its potential for unintended and off-target harm, its irreversibility and its hard-to-calculate long-term consequences. It is also too early to be clear how much the cited benefits are hype or are justified.

Huang's team found: *'a surprising number of 'off-target' mutations assumed to be introduced by the CRISPR/Cas9 complex acting on other parts of the genome. This effect is one of the main safety concerns surrounding germline gene editing because these unintended mutations could be harmful. The rates of such mutations were much higher than those observed in gene-editing studies of mouse embryos or human adult cells. And Huang notes that his team likely only detected a subset of the unintended mutations because their study looked only at a portion of the genome, known as the exome. 'If we did the whole genome sequence, we would get many more.'*<sup>20</sup>

### **ii. (Un)fair allocation of resources**

The cost of healthcare is rising, with no end in sight. Investment in one area of healthcare inevitably necessitates explicit or hidden disinvestment in other areas.

Fairly distributing healthcare spending is exceptionally difficult. Allocation of resources should not reflect the power of interest groups but should reflect need. Those in most need of healthcare, the elderly and those with chronic conditions, are often the groups who suffer from the most neglect and ill-treatment (evidenced in several official reports). Others may suffer from unnecessary and intrusive over treatment (reflected in patterns of over-prescription from sedatives to antibiotics). The tendency to overtreatment is, at least in part,

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<sup>17</sup> <http://www.bailii.org/ew/cases/EWHC/Fam/2015/2602.html>

<sup>18</sup> <http://nuffieldbioethics.org/wp-content/uploads/Genome-Editing-Briefing-Paper-Newson-Wrigley.pdf>

<sup>19</sup> The frequency of Cas9's off-target cuts varies widely from cell to cell and from one sequence to another. One lab has seen off-target sites with mutation frequencies ranging from 0.1% to more than 60%. Even low-frequency events could potentially be dangerous if they accelerate a cell's growth and lead to cancer.

<http://www.nature.com/news/crispr-the-disruptor-1.17673>

<sup>20</sup> <http://www.nature.com/news/chinese-scientists-genetically-modify-human-embryos-1.17378>

due to unrealistic desires and to a failure to face the reality of the limits of medicine and of human life.

Questions need to be asked about the possible diversion of public resources and attention away from those who have more need for healthcare, and away from ethical and more promising alternatives to germline editing (including DNA editing in somatic cells). To put it more bluntly, who will foot the bills?

The likely cost of creating ‘three parent embryos’ for mitochondrial disorders is striking: £80,000 for each ‘treatment’, which would be suitable for perhaps 10-20 women per year. This brings into stark relief questions about allocation of resources, considering that there are alternatives available, and in view of the significant ethical concerns with this ‘treatment’.<sup>21</sup>

For high profile, ‘cutting edge’ research, that attracts publicity, demand from individual patients can be driven by the media who are looking for narratives of women afflicted with genetic diseases. In such cases, stories of families with very difficult life situations (rightly) pulls at the heartstrings but (wrongly) can deflect attention from broader ethical and practical considerations and, in some cases, facts themselves, including whether they would be suitable for proposed treatments. **This can skew both funding, public support and regulation.**

### iii. Editing the germline and future generations

Ethical issues should not be narrowed down solely to considerations of safety. There are further issues with genetically manipulating the genome of humans not yet born.

As we also note above, this is understood by most other countries as well as many scientists, including – importantly - the Director of the US NIH who warns that altering the human germline in embryos ‘...has been viewed almost universally as a line that should not be crossed...the strong arguments against engaging in this activity remain. These include the serious and unquantifiable safety issues, ethical issues presented by altering the germline in a way that affects the next generation **without their consent**, and a current lack of compelling medical applications justifying the use of CRISPR/Cas9 in embryos.’<sup>22</sup> (emphasis added)

Germline editing would allow for changes to be passed down to future generations. Altering the genomes of our offspring — not just the first generation but all later ones as well— means **irreversibly changing** every cell in their bodies, forever. The risks of such biologically extreme experimentation would be huge, from the early stages of embryonic development through the life spans.

### iv. Longer term eugenic concerns

Germline research, if used for human treatments, is a bridge towards genetic enhancement, and eugenics, as several scientists warn in *Nature*:

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<sup>21</sup> [http://www.bionews.org.uk/page\\_604026.asp](http://www.bionews.org.uk/page_604026.asp)

<sup>22</sup> <http://www.nih.gov/about-nih/who-we-are/nih-director/statements/statement-nih-funding-research-using-gene-editing-technologies-human-embryos>

*'Such research could be **exploited** for non-therapeutic modifications...permitting even unambiguously therapeutic interventions could start us down a path towards non-therapeutic genetic enhancement.'*<sup>23</sup>

Eugenic concerns may appear to be far fetched and scaremongering, however anything that reinforces discrimination by improving human genetic traits should be vigorously opposed. Although after the Second World War the British rejected eugenics, that was not true of all.<sup>24</sup> Moreover, twenty-first century efforts to directly modify the human germline may play out differently, (driven by individual parental 'choice' not state control), but opening the door even a small way to the determination of 'bad' genes that need to be replaced and 'good' genes to be introduced would reflect criteria set by the economically and socially privileged. Of course parents influence their children in many ways but changing the genetic code is very different to other types of parental choices, not least because changes are to the fundamental genetic make-up of a person and are passed down future generations.

We are looking at more 'bottom-up' than the 'top-down', state-directed racial programs of the past: individuals and families choosing to edit their genes, whether to prevent illness or improve capacity in some way, and finding themselves encouraged to do so by the biotechnology industry.

There are already demands that we should not pass up the chance to make improvements to our species: *'The human genome is not perfect...It's ethically imperative to positively support this technology.'* Says John Harris<sup>25</sup> and, similarly, Julian Savulescu.<sup>26</sup>

Others warn that: *'...as we have seen with the American eugenics movement, fear of mental illness or other culturally driven preferences may lead some parents to decide to have their embryo's genome edited without fully understanding the complex genetic basis, if there is a genetic basis, behind these traits...We think the new technologies with genome editing will allow it to be used on individuals who aren't just interested in using IVF to have children but have healthier children as well, if there is a genetic disease in their family.'*<sup>27</sup>

## **v. Other ethical issues**

Other ethical issues must also be weighed in the balance.

- **Experimentation on embryos** in the course of developing the therapies
- **Discarding of embryos and abortion of fetuses** for whom the therapy is unsuccessful
- **Resources** (versus needs and alternatives)<sup>28</sup>
- **Social justice** (is this just for the socially and economically privileged who have access to benefits?)
- **Equity in distributing benefits**

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<sup>23</sup> <http://www.nature.com/news/don-t-edit-the-human-germ-line-1.17111>

<sup>24</sup> <http://www.cmfblog.org.uk/2016/01/15/designing-our-descendants-brave-new-britain-takes-the-lead-again/>

<sup>25</sup> <http://www.cmfblog.org.uk/2016/01/15/designing-our-descendants-brave-new-britain-takes-the-lead-again/>

<sup>26</sup> <http://www.telegraph.co.uk/news/science/science-news/9480372/Genetically-engineering-ethical-babies-is-a-moral-obligation-says-Oxford-professor.html>

<sup>27</sup> <http://www.nature.com/news/don-t-edit-the-human-germ-line-1.17111>

<sup>28</sup> For example, estimates that using mitochondrial donation techniques may cost £80,000 for each of the 10-20 women at risk of passing on a mitochondrial disorder raise concerns over whether this would be appropriate use of limited NHS resources or could such large sums be better spent researching actual treatments for mitochondrial or other disorders, affecting larger numbers of people?

- **A narrow focus** on ‘Western’ diseases
- **Patenting rights and commercialisation** increasing costs
- **Genetic manipulation of viruses** for weapons and warfare, when used with a gene drive<sup>29</sup> (see below)
- **Democratic consensus in decision-making** on the permitted scope of genome editing (is public debate driven by scientists and sections of the media?<sup>30</sup>)
- **Issues of public trust** and assessment of acceptable risk levels
- **Public fear of ‘GM babies’**
- **Consideration of philosophical issues**<sup>31</sup>

## vi. Alternative options

We appreciate the primary, and persuasive, public arguments for permitting germline research, that it may benefit those with debilitating disorders (assuming it is tightly regulated and controlled), but as we have said above, there are other ways that this can be done – either through prenatal genetic diagnostics, donation of gametes or indeed somatic cell editing. All are safer options for parents who carry mutations for a disease.

Germline editing is not the only option for therapies, particularly given the dangers to the health of future generations from using this research in humans, without knowing the precise effects of genetic modification until after birth. Even then, potential problems may not surface for years.

Society has a choice as to how it spends funds and where it directs research, and needs to weigh all the risks and benefits. We are calling for caution, for ethical decision-making and for the protection from irreversible risk for future generations from germline engineering.

### **1.6 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?**

We consider international and national legal frameworks are essential. Science must operate within boundaries and scientists should not be seen to be above the law (see above).

Of course, biotechnology research is global, employing millions of people but if both the US and UK agree to prohibit germline editing, it would strongly influence researchers elsewhere in the world.

Many scientists, including one of CRISPR’s inventors, want a moratorium on editing germ line cells, which we fully support.

### **Is there a military interest in genome editing research? What is its nature?**

We caution scientists and legislators about the potential for biological warfare using these techniques. If CRISPR is used with a ‘gene drive’,<sup>32</sup> genes become self-propagating and could

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<sup>29</sup> <http://science.sciencemag.org/content/345/6197/626>

<sup>30</sup> <http://www.cmfblog.org.uk/2015/09/18/in-five-years-time-or-less-expect-to-see-the-uk-permit-the-creation-of-gm-babies/>

<sup>31</sup> [http://www.bionews.org.uk/page\\_523365.asp](http://www.bionews.org.uk/page_523365.asp)

cause a great deal of irreversible harm in a population. Genetic modification is hard to detect but would be relatively easily transmissible. The material for using CRISPR is straightforward to obtain, assemble and experiment with, by amateur scientists, but this also creates potential to be abused.<sup>33</sup> We note that DARPR have concerns with this too.<sup>34</sup>

### **1.7 What other important questions should or might we have asked in this section?**

The key question that was not asked is whether making *germline* genetic changes, that can be inherited, should be carried out or not. This should have been clearly distinguished from genome-editing techniques in *somatic* (non-reproductive) cells. The former is the focus of our concerns in this submission, while the latter is a promising area of therapeutic development.

*'The vast majority of genetic and other diseases can be addressed by gene editing of these somatic cells and do not require modification of germline cells... This is the greatest area of patient need, where the benefits and risks are best understood, and where the ethical support is unambiguous.'*<sup>35</sup>

Questions around the danger of eugenics should also have been asked, in the light of calls by some to improve our species by enhancing our genome, and warnings by others of opening the door to eugenic practices by scientists

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Christian Medical Fellowship  
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<sup>32</sup> Which can quickly propagate an edited gene through a population., but has huge risks too.

<http://science.sciencemag.org/content/345/6197/626>

<sup>33</sup> <http://www.gizmag.com/home-crispr-gene-editing-kit/40362/>

<sup>34</sup> <https://www.broadinstitute.org/news/7263>

<sup>35</sup> <http://crisprtx.com/1130%20CRISPR%20-%20INTELLIA%20CRISPR%20TX%20POSITION%20STATEMENT.pdf>