Gene Editing: A New Legal Frontier
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Introduction

Today is the third and final lecture in my series this year.

I'm going to talk to you about the new gene editing technology that gives us the ability to change our DNA – removing, adding and replacing parts of our genetic code.

I'm going to focus on *human* gene editing, but there are many other uses beyond this.

I am going to start by giving you a brief explanation of *what* we mean by 'gene editing', although I will avoid making it too scientific!

Then I want to outline the range of uses to which we might put the technology:

- What we're doing now
- What we might be able to do in the future.

From there, I want to explore some of the benefits of the technology, and some of the potential impacts that might want to give us pause.

As ever, I will try to steer you through the issues and give you food for thought, rather than trying to convince you of a particular position to take.

I'll also weave in some explanation of the way regulatory systems have responded, both nationally and internationally.

What is Gene Editing?

Gene 'editing' has developed rapidly over the past 10-15 years. When people talk about 'new gene editing' technology, what they mean is the recently developed technologies that are much more precise (and hence have much more powerful potential).

Gene or genome editing technology means a method that allows changes to be made to someone's DNA.

Changing someone's DNA could:

- Change their traits where these are caused by genes (which almost everything is, in combination with things that happen to us, like what we eat, what we're exposed to, what we do with our bodies etc.)
- This might include:
    - Eye colour
- But our DNA also affects things like whether we are likely to get a disease, so editing our DNA might
    - *Reduce* risk of developing a disease
        - E.g. a disease where our genetics *predispose* us to it but don't definitely mean we will get it
    - *Remove* our disease risk
        - E.g. if we could edit out all the genetic factors in a disease

- Simpler with diseases that are caused by only one genetic mutation

We have had the ability to edit the genome for decades, but it hasn't been very precise.

New Gene Editing Tools

In the past twenty years, new tools have been developed that allow scientists to 'cut' DNA sequences at a particular spot, and then remove DNA, add some, or replace some.

They cut the DNA sequence with an enzyme known as an 'engineered nuclease'.

A nuclease is a type of enzyme that can break the bonds that hold DNA together.

So when they've been engineered, we can direct them to break particular bonds. These nucleases act like 'molecular scissors' and cut through both strands of DNA.

There are a number of types of nucleases used in gene editing, and the number is growing:

- Meganucleases
- ZFN
    - Stands for 'Zinc Finger Nucleases'
- TALEN
    - Stands for 'transcription activator-like effector nucleases'

We have been able to introduce new genetic material into organisms for decades, but with little precision.

These new technologies are exciting and important because of their *precision*.

- Can focus on very specific sequences
- Don't run the risk of missing the sequence we intend to target

The big break through you might have heard of, which is one of these technologies, is CRISPR-Cas9

What is CRISPR-Cas9?

- CRISPR stands for 'clustered regularly interspaced short palindromic repeats'
- It was innovative and important because it made it a lot easier to edit DNA
    - It's faster
    - It's cheaper
    - It's more accurate.[1]

Very important is that it enables genome editing *in vivo* – i.e. inside the organism's body – cheaply and with precision.

It is a huge step forward from earlier genome editing tools because it is so highly selective and efficient.

The CRISPR system is based on a naturally occurring bacterial genome editing system.

CRISPR elements can be found in many bacteria. The bacteria use them to find and destroy pathogens. Specifically, it destroys *nucleic acids* from those pathogens (i.e. bits of genetic material) when the pathogens invade the bacterium.

For example, the Streptococcus bacterium uses its CRISPR system to identify and cut up the DNA within viruses, thereby destroying them.

To do this, the CRISPR system identifies a specific part of the pathogen DNA which it will then target. It does this by using gRNA or 'guide RNA' – small bits of RNA, which match and bind to the part of the DNA of the pathogen that will be attacked.

Once the gRNA has bonded with the DNA, the whole thing binds to the CRISPR-associated (Cas) nuclease, which cuts the DNA at a spot essentially marked by the gRNA.

[1] https://www.genome.gov/about-genomics/policy-issues/what-is-Genome-Editing

So the nuclease (Cas9) is cutting the DNA where the gRNA tells it to. It's like a genetic template with molecular scissors.

What is crucial is that we can introduce *synthetic* gRNA – so we can, via this, *choose* the part of the DNA that the nuclease will bind to, and hence determine where the cuts will be made.

Scientists had known about CRISPR for some time, but the big leap was the discovery of the Cas9 nuclease. Unlike TALENs and ZFNs, Cas9 nucleases can be given different targets by changing the guide RNA (rather than editing the protein itself).

We can use the CRISPR system to:

- Knock out sections of DNA
    - Cut out a part
- Knock in sections of DNA
    - Cut the DNA and insert more
- Activation and inhibition
    - CRISPR can be used to also *deliver* other proteins to a particular site on the DNA and rather than removing a section, it either *activates* or *inhibits the activation of* that sequence
- Screening
    - It can also be used as a tool to screen lots of potential candidate genes (for research purposes)

That's very simple – I'm not a scientist!

CRISPR-Cas9 system had been discovered decades ago, but it the early 2010s that it was developed into a tool that could be used for gene editing. The two key scientists involved - Emmanuelle Charpientier and Jennfer Doudna -- were awarded the Nobel Prize in Chemistry in 2020.

What Can Be Edited?

Which DNA is edited is also important, and the ethical issues that arise differ depending on *what* we edit, *where* and *in whom.*

To break it down:

There is a difference between editing DNA in *somatic* cells (i.e. most of the body's cells) and *germline* cells (that is, the DNA that is passed on during reproduction – eggs, sperm, fertilised eggs).

There are two important differences here:

1. Any change to a germline cell that is then fertilised (or allowed to develop into an embryo) will affect *every* cell of that organism
    - All will carry the changes
    - Whereas changes to somatic cells only affect the edited cells
        - No other cells are affected
2. Those changes will be handed down to any children the person has.
    - Whereas changes to somatic cells are not passed down to future generations

Relatedly, the other key distinction is editing cells in an *embryo* that has yet to become a full, legal person, and editing those in a *person*

- We might just be editing cells *in vitro* with no intention of them entering a person, or becoming a person
    - Pure research
    - The sort of thing we'd be doing in disease modelling in research

- If the person is an adult, then their consent would be needed
- If the person is a child, then we would have to decide whether doing so is in their best interests
- This is true of embryos, too, but the issues are more complex, as we will see
    - But if they are not yet a legal person, the legal approach might differ
    - There are complicated issues around whether we should regard an embryo as a person
        - It matters because either we're *changing* a person, or we're *making* a different person

And it was a case of the latter kind of change that gene editing hit the headlines in 2019 when He Jiankui reported that he had edited the genes of two embryos.

Jiankui edited the genomes of two embryos in an attempt to afford them genetic resistance to HIV using CRISPER-Cas9.

Jiankui's work was met with approbation when it was made public, from the science community and philosophers. He was fired from his position and ultimately jailed by the Chinese authorities.

These events spurred national and international responses, particularly the formation of the World Health Organization Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing, which took on the task of examining "the scientific, ethical, social and legal challenges associated with human genome editing (both somatic and germline)" in December 2018.

There were also various legal responses, to which we will come, but as an example, the Chinese Government criminalised practices related to gene editing.

Before we delve into this complex set of issues, let's take a pause and look at the great range of uses for human gene editing.

I'll try to clarify what we can do *now* and what *might* be possible in the future.

Uses range from basic research to applied biotechnology and biomedical research, treatments and enhancement.

What Can It Do Now?

Research use for understanding gene function

Scientists can modify genes in a highly targeted way using genome editing tools (such as ZFNs, TALENs, and CRISPR/Cas9).

- Gives them a very powerful method to analyse gene function
- They can, for example, change a single gene in an animal and then study it to see what that gene does (by seeing what happens when it has been 'knocked out')
    - Example: The Burgess Lab in the United States studies deafness by focusing on genes in zebrafish that are involved in hearing. It knocks out different genes and then studies function[2]

Disease modelling

Because gene editing enables scientists to precisely manipulate cellular behaviour and function.

- Enables them to create very precisely genetically engineered animals and by studying them, they can understand how various diseases work
    - An example is the development of models for studying cardiovascular disease
        - CVD is usually associated with a single genetic mutation, so it's a good target for this sort of research
        - Scientists create models that enable them to analyse the pathogenic genes involved in causing CVD

[2] https://www.genome.gov/about-genomics/ policy-issues/what-is- Genome-Editing; https://www.genome.gov/staff/Shawn-Burgess-PhD

        - They can then use these to test how well a gene therapy can affect gene expression and function, which might enable them to create a treatment[3]
- This sort of research can then be used to develop therapies and treatments much more effectively
    - An example is the development of tumour-targeted T-cells[4] that could be used in the treatment of cancers

Testing treatments and drugs

Relatedly, gene editing can enable researchers to create models for testing drugs, and even test animals that have been genetically edited to create an animal model for drug or treatment testing.

- An example is the creation of mice developed to test a gene therapy for diabetes.

Creating treatments

The goal of this research is to develop gene therapies that can be used to remove disease-causing genetic sequences and replace them with non-disease causing sequences.

- Example is therapies that attempt to alter gene sequences that cause Alzheimer's disease

One successful example is the treatment of leukaemia in children

- Layla Richards – was successfully treated with genetically edited immune cells, which eradicated her leukaemia – the cells had been edited to make them able to destroy the cancer cells
    - Treated at Great Ormond Street
- Other children treated since then

One clinical trial uses CRISPR to correct the genetic mutation in a patient's blood stem cells, which when infused back into their body, then produce healthy blood cells.

These would include treatments for:

- Cancers
- Genetically-influenced disorders
    - Neurodegenerative disorders
- Viral diseases
    - A recent success in relation to viral diseases is the treatment of HIV
    - Researchers have created a genome editing-based HIV therapy that modified genes related to the infection to create HIV-resistant CD4+ T cells, which were then infused into patients to help them fight off HIV.[5]

What might it be able to do?

Cancer treatment

It might eventually enable doctors to remove malignant mutations and replace them with normal DNA sequences. [6]

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[3] REVIEW ARTICLE OPEN Applications of genome editing technology in the targeted therapy of human diseases: mechanisms, advances and Prospects Hongyi Li1, Yang Yang1, Weiqi Hong2, Mengyuan Huang2, Min Wu3 and Xia Zhao1

[4] REVIEW ARTICLE OPEN Applications of genome editing technology in the targeted therapy of human diseases: mechanisms, advances and Prospects Hongyi Li1, Yang Yang1, Weiqi Hong2, Mengyuan Huang2, Min Wu3 and Xia Zhao1

[5] REVIEW ARTICLE OPEN Applications of genome editing technology in the targeted therapy of human diseases: mechanisms, advances and Prospects Hongyi Li1, Yang Yang1, Weiqi Hong2, Mengyuan Huang2, Min Wu3 and Xia Zhao1

[6] REVIEW ARTICLE OPEN Applications of genome editing technology in the targeted therapy of human diseases: mechanisms, advances and Prospects Hongyi Li1, Yang Yang1, Weiqi Hong2, Mengyuan Huang2, Min Wu3 and Xia

It might produce immunotherapeutics that use genetically engineered immune cells to fight cancers.

What Ethical Issues Does it Raise?

Treating Disease

Enhancement

Controversies

- Editing embryos
    - Open future
    - Consent
        - By parents?
    - Limits on what can be changed
        - Non-disease traits?
    - Impact on future generations – germline edits
    - Health inequities
    - Impact on parent / child relationship?

Health Inequities

Human Enhancement

Now that we have the ability to edit our genome, that means we can not only treat disease, but we might also make amendments that *enhance* us.

What Does It Mean to Enhance Ourselves?

- Return to normal functioning?
- Bring everyone up to a set level?
- Increase everyone's capacity by the same amount?
- Give capacity beyond the norm?

And What Would We Enhance?

- Only some traits?
- All traits?
- Would there be any limits?
- Physical
    - Body changes
    - Capacity to stay awake?
- Cognitive
    - Brain capacity
    - Combat fatigue
- Emotional
    - Empathy

Arguments against enhancement

- Problematic consequences

- Unknown harms
    - Changing the germ line?
    - Status quo bias
    - Example: raising average IQ
- Signaling harms to the disabled
- Reduction human variation
- Expectation to enhance → pressure to do so
- Stratification

Let's look at a few of these.

Impact on Parent / Child Relationship

One concern raised about editing children (and this would apply to embryos) to enhance them is that it would adversely affect the parent/child relationship.

Michael Sandel (again) argues that there is value in *not* being able to design our children.

> "In a social world that prizes mastery and control, parenthood is a school for humility. That we care deeply about our children and yet cannot choose the kind we want teaches parents to be open to the unbidden. Such openness is a disposition worth affirming, not only within families but in the wider world as well. It invites us to abide the unexpected, to live with dissonance, to rein in the impulse to control."

He argued that we need to appreciate children 'as they come' – accepting love – implications for parental relationship

- It enriches that relationship to be one that is not designed

Arguments in Favour of Enhancement

Having looked at the downsides, let's look at some of the reasons that we *would* want to improve our genetic makeup

- Improve quality of life
- Give people experiences they might not have
- Reduce risks of harm to self
    - E.g. in workplace
- Increase capacities
    - In workplace
    - In social life (e.g. empathy)

Some philosophers have made some important points we should consider when thinking about whether it might be right to enhance.

Guy Kahane and Julian Savulescu point out that:

- Some objections to enhancement rest on errors – often because of focus on extreme enhancement (which is not likely)
    - enhancements typically modulate naturally existing substances and processes → affect don't lead to radical change and distortion
    - Enhancements work largely on natural processes / substances (which are probably not set at optimal levels (due to blind processes)
    - Human variation within normal range means many people are not at optimal level

So when we want to think about enhancements, we need to think carefully about whether the benefits are worth any risks or downsides.

In doing so, we also have to account for what we can and can't control.

Kahane and Savulesu note that

- It is a common objection that biomedical interventions have both positive and negative effects
    - → This is not an argument against enhancement but, rather, an argument for more precisely *fine-tuned* enhancement

They are right – we shouldn't see this as a simplistic 'it might be good, it might be bad' issue

- We need to look closely at what we can control, and the implications of the changes we make
- Weigh their costs carefully and precisely
- Don't make unconsidered changes

Michael Sandel raises a concern, however, about the very idea of enhancement and it's impact on our sense of self:

> "The deeper danger is that they represent a kind of hyperagency—a Promethean aspiration to remake nature, including human nature, to serve our purposes and satisfy our desires. The problem is not the drift to mechanism but the drive to mastery."

But as Savulescu and Kahane point out, the natural level isn't natural at all

- Therefore we have already shifted it – it is open to further shift (or shifting is not inherently problematic)

And further, just because something is natural, does not mean it is necessarily good.

- We clearly don't think that, or we wouldn't treat diseases
    - We would always accept our lot and be ok with it
    - We actually do precisely the opposite.

Sandel may have a point, but is that point strong enough that we should reject a means of genuinely improving our lives? And those of others?

Mike Parker reflects some of Sandel's thinking when he says

> *"Both aspects of our lives are interwoven and, indeed, it is this interweaving and our struggles with it that make us what we are and constitutes in its interplay of light and dark, much that is of value and significance in human existence"*

Savulescu and Kahane respond:

> *"Some people have a lot of light and no dark; others are all dark. The issue is whether we should accept what nature delivers up or make a choice."*

The key thing is to consider *what* we want to enhance and *why* and *what the costs might be*.

Germline Genome Editing

After He Jiankui's work was revealed, there were public calls for a moratorium on the implantation of gene edited embryos.

For example, Feng Zhang of Broad Institute of Harvard and MIT made such a call at a public event on 'Altering the Human Genome' at Harvard Kennedy School.

He explained the need for this as follows:

> *"The moratorium is a pause. Society needs to figure out if we all want to do this, if this is good for society, and that takes time. If we do, we need to have guidelines first so that the people who do this work can proceed in a responsible way, with the right oversight and quality controls.'*[7]

Germline genome editing poses *particular* problems because any changes we introduce in this way will remain in the population

- They will be passed on

[7] https://news.harvard.edu/gazette/story/2019/01/perspectives-on-gene-editing/

In essence, they become a permanent part of our collective gene pool.

They will affect the type of people who are born in the future.

And once it's been done, it may be very difficult to reverse.

So unlike changes made to somatic cells, germline changes arguably affect us all as a community (nationally and globally).

Which is why Zhang rightly calls for pause to consider, and to think about this collectively.

How, then, should we think about this particular question?

We might think "better not to risk it, as there might be unexpected drawbacks that we can't fix".

Or we might think "the potential benefits are worth the risk!"

How can we work out what to do, particularly when the question is necessarily so speculative:

- We can see some benefits, but not all
- We can imagine some drawbacks, but there may be many that are unforeseen and unforeseeable
- But that might be true of the benefits, too.

And there are also considerations such as:

- Will the benefits be shared with everyone?
    - It may take a long time and thereby initially result in inequities
        - If the technology is expensive, these are likely to compound inequities that already exist
- What will we do about very bad drawbacks?
    - Who should bear the burden?
    - If the government decides to allow this, shouldn't they facilitate redress?
- How will we control it?
    - What if one country does it and others do not?

There are a very large number of questions.

Removing mutations associated with disease or disability

One thing amending the germline might achieve is to *remove* the genetic mutations that cause disease or disability

- If done enough, they would be eradicated in the population
- Or at least reduced
- Families would no longer pass them down to their children
- Carriers would not bear the burden of being worried about reproduction

For conditions that are life-limiting, or very difficult to manage or cope with, editing them out of the population might be welcome.

- And because we are not doing this via *abortion* or *embryo selection* we avoid a lot of the moral problems these methods raise
    - We really are selecting against *the disease* not the person with the disease

This approach presumes that disease and disability are *harms*

It is focused on the downsides of disease and disability. We can easily imagine what is meant

- Painful conditions
- Life-limiting conditions

- Conditions associated with restrictions on behaviour

For things we class as diseases, this might be reasonable straightforward

- Predispositions to cardiovascular disease
- Huntington's disease
- Early onset dementia

We could list hundreds, thousands. And if gene editing could prevent anyone having to suffer them, that seems straightforwardly a good thing to achieve.

But this becomes murkier when we move to consider things we tend to think of as disabilities, rather than diseases.

Often, we understanding disability as a harm.

So here is Janet Radcliffe Richards taking this view (in relation to selecting embryos)

> *"It is hard to doubt that most people must regard disability as having negative value. However strong their all-things-considered commitment to any or all existing disabled people, however willing they are to do all they can to make life as good as possible for them, and even though they would not change their existing disabled child or spouse or colleague for any able-bodied person in the world, the fact remains that most people would think it better for themselves if their disabled friends and relations and employees were not disabled."*

But not everyone shares this view, and it is not so simple to say that anyone with anything called 'a disability' necessarily would prefer not to have it (and in the case of germline editing, never to have had it and for others not to have it).

Disability Eradication as Discrimination

Nor is it so simple to say we should simply wipe it out of the gene pool

- Is it right to eradicate the condition?
    - Where the condition is a 'disability' or a 'difference', it would be lost to the world
        - Down syndrome
        - Autism
    - Might our world is less rich and diverse?
    - What message do we send to people living with that condition?
        - For some, we might be saying that condition is one that is not to be valued, but avoided.
        - For many people with disabilities, not least those in the Down's syndrome community, considerable hurt and distress has been caused by the law's attitude to the eradication of disability
        - There was similar backlash to the announcement of further studies into the genetic basis of autism

This slide is from the Don't Screen Us Out campaign against *testing* for Down syndrome in pregnancy (with a view to termination) but the point is the same

- Heidi Crowther, you can see there, argued in her legal case, that the approach to screening for disability under the Abortion Act was discriminatory
    - Disability as a basis for termination
- We could make the same argument in relation to gene editing

Social Model of Disability

And before we consider editing out differences and disabilities, we would at the very least want to notice too whether they are disabilities merely because we do not accommodate their difference.

as Mike Oliver argues here, it's not really a disability but rather a failure of society to accommodate a range of different persons.

> *"it is not individual limitations, of whatever kind, which are the cause of the problem but society's failure to provide appropriate services and adequately ensure [that] the needs of disabled people are fully taken into account in its social organization".*

- ADHD
- Autism
- This draws on the Social Model of disability

Disability as a Good

And even more importantly, before we start thinking we should eradicate things, we might want to think whether some of these things we've labelled 'disability' or 'disease' are actually conditions people might *value.*

- They might individually value them
- We as a society might value having people with these genetic makeups with us

Greta Thunberg describes her autism as her superpower because of the clarity and focus it gives her.

- Her black and white thinking is what led to not to ignore the truth she saw around her and act on it

Here is Charles Foster on his son's dyslexia:

> *'I can't bring myself to say that his dyslexia is pathological. To use the old, deeply inaccurate language of brain lateralization, he's a right brain person. He sees holistically; he's a big picture person; he intuits; he connects wildly distant and different concepts. …*
>
> *When I see a tree, it's clothed with other peoples' written descriptions of trees. The tree itself is more or less invisible. But not for Tom. There's nothing vicarious about his world. He sees for himself, and seems to see far more of the real tree than I do. Not for him the neat, prescriptive relationship between word and reality that defines and suffocates me.'* [8]

So, this isn't to say we shouldn't decide to edit out some things, but merely that we need to think carefully about what we edit and why we're doing it, if we are going to permanently change our collective gene pool.

Conclusion

Gene editing technology offers enormous promise to help us end disease. But it will be complex to navigate the ethical issues it raises. We must step towards the future carefully, and considering all aspects of the impact of the technology rather than proceeding too hastily, to our cost.

[8] https://www.charlesfoster.co.uk/?p=590; https://www.charlesfoster.co.uk/?p=690