POLICY BRIEFING

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Somatic genome editing: ethics and regulation

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The therapeutic applications promised by a new generation of genome editing techniques, such as CRISPR, could transform healthcare. However, enthusiasm for clinical genome editing must be tempered by regulatory oversight and underpinned by ethical debate. Here we explore key ethical considerations, and how the regulatory landscape is evolving in response to technological development.

Summary

- The potential benefits of somatic genome editing therapies justify innovation and research. However, ethical and regulatory challenges must be addressed now, as the process of developing regulation is slow and subject to wider public debate
- The ethical considerations raised by somatic genome editing are similar to those raised by existing gene therapies. These include ensuring patient safety, distinguishing between therapy and enhancement applications, and ensuring fair access to treatments
- Changes may need to be made to the regulatory pathway for genome editing therapies from clinical trial through to post-authorisation, as methods and safety related issues are diverse and unique
- There are no specific provisions for genome editing within the legislation governing it and, while the regulatory framework is evolving, it may not be sufficiently flexible for these new therapies

Genome editing can be performed in germline cells (sperm, eggs or embryos) to induce heritable genetic changes or in somatic cells (other cells) to induce non-heritable changes. Somatic cell editing is much closer to clinical implementation, yet has received far less media attention. In this series of briefings we consider different aspects of somatic genome editing.

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Ethical considerations

Individual and wider societal concerns raised by somatic genome editing broadly mirror those that have arisen in response to other gene therapies:

Safety and the avoidance of harm

The ethical application of genome editing relies upon a risk/benefit ratio that ensures a beneficial outcome for the patient. Modern genome editing tools may alleviate some safety concerns due to the targeted nature of the technology, but others persist, such as the potential for off-target effects, where genome editing occurs at unintended sites with potentially harmful consequences for healthy gene function.

Treatment or enhancement?

There is no clear distinction between therapy and enhancement. Both share the goal of conferring improvement, although enhancement is commonly understood to refer to 'changes that alter what is 'normal,' whether for humans as a whole or for a particular individual.'[1] However, what is considered to be normal is ambiguous and changes over time, and there is debate surrounding whether deviation from normality constitutes 'disease'. For example, within the deaf community many people reject the notion that deafness is something that needs to be 'cured'. Consequently, identifying which diseases are sufficiently serious to warrant editing must take account of different views, and existing alternative treatments.

The public are predominantly supportive of using somatic genome editing for therapy, although a majority are also resistant to its use for enhancement purposes[2], a view echoed by the National Academy of Sciences in their report on human genome editing[1]. However, as societal tolerance increases, enhancement applications may emerge. For example, a hypothetical treatment might initially be used to reduce cognitive decline in a patient with Alzheimer's disease, then for prevention in someone at high risk of disease, then eventually to boost the cognitive faculties of a healthy individual.

Ensuring fair access

The philosophical concepts of justice and fairness that underpin a fair society suggest that social goods should be distributed to offset existing social inequality[3]. Genome editing could be used to help those disadvantaged by painful conditions and severe disability, but therapies are likely to be expensive . Distributing benefits equitably will be a challenge, and realistically the NHS may be unable to fund all genome editing treatments for serious disease. Who will decide which treatments are funded, and based on what criteria? Could access through private providers exacerbate health inequalities?

Despite these concerns, somatic genome editing holds great promise for the treatment and prevention of serious diseases, especially where reasonable alternative treatments are not available. This potential has led some commentators to argue that provided the technology is proven to be safe and effective, some applications of genome editing are not just morally permissible, but moral imperatives[4].

The legal and regulatory landscape

How is somatic genome editing regulated in the UK?

Genome editing poses a challenge to regulators as approaches vary considerably depending on the tissue of origin and how the therapy will be utilised. Therapies using somatic genome editing are classified as Advanced Therapy Medicinal Products (ATMPs) – i.e. medicinal products comprised of genes, tissues or cells – and governed under the ATMP Regulation[5] . The technical requirements laid out by this legislation are high level because the type and amount of data necessary to demonstrate the quality, safety and efficacy of diverse ATMPs is highly specific. They are further explored in class-specific guidance developed by the European Medicine's Agency (EMA).

All medicines must be authorised before they can be made available to patients. Whilst a majority of medicines are authorised at a national level, a centralised procedure overseen by the EMA is compulsory for ATMPs to ensure availability across member states through a single licence, speeding up patients' access to these treatments. This requires that applications are assessed by the EMA's scientific committees and authorised by the European Commission (EC).

Is the current regulatory framework fit for purpose?

The legal and regulatory framework for ATMPs[6] has been in place in the EU for over a decade. However, rapid advancements in highly personalised innovative therapies, such as genome editing, are challenging the existing framework and guidance.

Whilst there are no plans to revise the legislation underpinning ATMPs , a need for adaptation has been recognised by the EMA and EC, who released a joint action plan for fostering future ATMPs in December 2017. This included holding an expert meeting to discuss critical regulatory issues and uncertainties associated with genome editing products, and publishing new guidelines and updating others, to ensure that "the regulatory framework supports —and not hinders — the development of ATMPs":

- **Guideline on quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells.**
  This addresses how the unique starting materials and manufacturing processes used in genome editing can enable precise gene modifications through identifying and controlling modified cells

- **Draft guideline on quality, non-clinical and clinical requirements for investigational ATMPs in clinical trials.**
  Clinical trial authorisation occurs at a national level, however the EMA ensures that market authorisation requirements are met and highlights that the distinctive development pathway for ATMPs might require the majority of non-clinical data to be available before human exposure

- **Draft guideline on safety and efficacy follow-up and risk management of ATMPs.**
  By their nature, ATMPs are innovative products whose safety and efficacy may not always be fully known at the time of approval. This guideline places increased emphasis on post-authorisation oversight of ATMPs to detect and mitigate against possible risks, which sometimes requires additional safety and efficacy studies

These guidelines operate against a backdrop of tools, exemptions and accelerated pathways introduced by the EMA to increase flexibility, facilitating the development of genome editing therapies. For example, it is recommended that companies adopt a risk-based approach during development. This allows developers to deviate from EMA guidelines where requirements are redundant and other strategies more relevant to establish the quality, safety and efficacy of the product under study.

More recently, the EMA's priority medicines (PRIME) scheme was introduced in 2016 as an expedited pathway for medicines addressing serious diseases with high unmet medical need (e.g. T cell cancer immunotherapies). Genome editing therapies often both lack the complete clinical data needed for full market authorisation and lend themselves to the unmet need requirement.

Overcoming barriers

The EMA are committed to facilitating bespoke accelerated development of novel therapies, including genome editing, but considerations also include minimising barriers to authorisation while maintaining public trust and confidence.

Significant activity in the ATMP field does not equate to therapies being available for patients. As of early 2019, only 13 ATMPs have received an EU marketing authorisation (four of which have been withdrawn). This number is set to grow as products employing CRISPR undergo clinical trials, but those that achieve authorisation struggle with reimbursement – a challenge likely to disproportionately affect genome editing therapies approved for small numbers of patients.

Despite the EU regulatory framework evolving to provide some flexibility for these new therapies, this may be insufficient once these medicinal products are used at scale, beyond the exemptions that currently enable their use. The challenge will be to build a regulatory and ethical framework that allows the development and use of these products at scale, while meeting quality and safety standards, and complying with ethical boundaries that society deems appropriate.

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