NUFFIELD COUNCIL ON BIOETHICS

Genome editing

an ethical review - *a short guide*

This is a short guide to *'Genome editing: an ethical review'*, published by the Nuffield Council on Bioethics in September 2016. The review considers the impact of recent advances in genome editing, which have diffused rapidly across many fields of biological research, and the range of ethical questions to which they give rise. This guide sets out some of the issues, themes and conclusions that are discussed in more detail in the review, which is available on the Council's website at www.nuffieldbioethics.org/genome-editing-review.

The review was carried out by an interdisciplinary Working Group that included expertise in science, law, philosophy, ethics, sociology and industry. In coming to its conclusions, the Working Group invited contributions from a wide range of people, including through an open call for evidence that ran from November 2015 until February 2016.

The next stages of this programme of work will focus on examining and addressing the ethical and practical questions arising in two contexts where genome editing may have a significant impact: firstly, the avoidance of genetic disease and, secondly, livestock farming. Reports on each of these two areas, with recommendations for policy and practice, will be published in 2017.

Contents

Genome editing in brief:

what, why and how?

What do we mean by 'genome editing'?

Almost all cells of any living organism (e.g. a human, animal, plant, bacterium) contain DNA, a type of molecule that is passed from one generation to the next during reproduction. DNA is involved in many essential biological processes including building cells and controlling their number and type, the production of energy, the regulation of metabolism, and fighting disease.

The term 'genome' generally refers to the entire sequence of DNA of an organism. The genome includes genes: sequences of DNA with specific functions that are involved in the production of the proteins needed to carry out many biological roles. It also includes regions of DNA that promote or inhibit gene activity, and regions that do not appear to affect protein production or function.

Genome editing is the deliberate alteration of a selected DNA sequence in a living cell. A strand of DNA is cut at a specific point and naturally existing cellular repair mechanisms then fix the broken DNA strands. The way they are repaired can affect gene function and new DNA sequences can be delivered when the DNA is cut and act as templates for generating an altered sequence. Genome editing techniques can be used to delete sections of DNA or alter how a gene functions: for example, by changing a variant that may give rise to disease to one that functions normally.

How does it work?

Genome editing techniques make use of certain proteins that can cut DNA in a precise, targeted location. Although this family of proteins was discovered in the 1960s, it is only since around 2005 that the ability of some of them to make precisely targeted cuts at almost any position in the genome has been recognised and utilised by scientists.

Among the recent genome editing technologies, CRISPR-based methods are particularly promising owing to their relative efficiency, low cost and ease of use, and the prospect of making edits at multiple sites in the genome in a single procedure.

What is CRISPR-Cas9?

CRISPR-Cas9 is a widely used genome editing method. It has two components. CRISPR stands for 'clustered regularly interspaced short palindromic repeats'. This refers to the basis of the 'guide system' that finds the 'target' – the specific sequence of the DNA that is to be modified. Cas9 stands for 'CRISPR-associated protein 9', the protein that cuts the DNA at the target site. CRISPR-Cas9 systems that target specific sequences can be produced relatively easily in a laboratory, or obtained in the form of commercially available kits that can be purchased online.

What is genome editing used for?

Most uses of genome editing have so far been in scientific research, for example to investigate models of human disease. However, the potential applications of these techniques are much wider than just research. Given that genome editing has the potential to alter any DNA sequence, whether in a bacterium, plant, animal or human being, it has an almost limitless range of possible applications in living things.

Areas of research and possible applications include:

- **Crops and livestock** (e.g. increasing yield, introducing resistance to disease and pests, tolerance of different environmental conditions)
- **Industrial biotechnology** (e.g. developing 'third generation' biofuels and producing chemicals, materials and pharmaceuticals)
- **Biomedicine** (e.g. pharmaceutical development, xenotransplantation, gene and cell-based therapies, control of insect-borne diseases)
- **Reproduction** (e.g. preventing the inheritance of a disease trait)

We expand on these areas in relevant sections of the review.

For more information please see Section 1: Genome editing

The context of genome editing

Genome editing and emerging biotechnology

The idea of making alterations to DNA is not new, and genome editing shares features with established techniques for genetic modification (e.g. those used to produce GM crops). From one point of view, genome editing is a technical development in this field: a newer and more precise tool for pursuing established objectives. From another point of view, however, genome editing could transform not only the field of biology, but the range of expectations and ambitions about human control over the biological world.

How we think about genome editing and its possibilities informs how the techniques will be developed, applied and controlled. In considering such matters, we must look at a number of factors that bear upon the emergence of genome editing as a technology, for example:

- The **conditions** under which it emerges, e.g.:
  - Economic and political conditions such as availability of research funding, influence of intellectual property regimes and government agendas
  - Social conditions such as cultural values and media representations.
- The **possibilities** for new biological interventions to which the technologies might give rise.
- The potential of these **possibilities** to create new opportunities and to change the ways in which we think about and address challenges such as in healthcare and food production.

Public interest

The public has an interest in genome editing, both in terms of its expectation of future social benefits, but also in possible costs and harms. It invests in it both financially (e.g. through state-funded research) and through the trust it places in scientists and innovators to help deliver the hoped-for benefits. More profoundly, there is a public interest in the ways in which different potential uses of genome editing might challenge and affect our moral and cultural values and understandings.

Impact on research

Genome editing, particularly the CRISPR-Cas9 system, has spread rapidly through the biological sciences. It offers a number of advantages: it is versatile, inexpensive, relatively easy to access (kits can be bought online) and to use (it requires biological expertise but does not require highly specialised knowledge or research skills), and it offers the prospect of making precise edits at multiple sites in the genome in a single procedure.

Its efficiency and specificity are comparatively high compared to other methods of genetic alteration,but are not without limitation. One challenge for researchers is the delivery of CRISPR-Cas9 into the target organism. It is often carried in inactive viruses, but there are limits to the size of an additional DNA sequence that a virus can effectively deliver. Another concern is the risk of 'off-target' editing at DNA sequences that were not supposed to be changed, though the techniques are continually being improved in this respect, and recent studies have demonstrated high specificity with no detected off-target effects. Strategies to reduce or eliminate mosaicism – where some cells in an organism have incorporated the changes and others have not – are also being developed.

We conclude…

Genome editing is having a transformative effect on biological research, in that:

- It makes it *possible and affordable* to do research that was previously not achievable; and
- It therefore *increases* the overall rate of research, including:
  - the amount of research that can be done within a set budget.
  - the speed of the research (increasing the overall rate, but also making it possible, for example, to complete in a shorter period of time the kind of project that would not have been possible before within a typical PhD or post-doctoral contract).

For more information please see Section 2: Science in context

Moral perspectives

Through our call for evidence, factfinding meetings and research interviews, we have identified a number of key moral perspectives on genome editing, which are briefly summarised below. These perspectives inform attitudes to the different potential applications of genome editing that we consider.

Science as a moral enterprise

This centres on the idea that the pursuit of scientific knowledge will benefit society, and that the freedom granted to scientists, and the trust placed in them by the public, is implicitly based on the expectation that science and technology will improve the conditions of human existence and of the wider environment.

Intervening in the genome

Few people argue that intervening in the genome is intrinsically more important than other ways of manipulating nature, but most acknowledge that it has significant and distinctive implications due to the role of the genome in determining biological processes and passing on changes to future generations.

Moral conservatism

Moral conservatism is often presented as a scepticism about the wisdom or motives of deliberate human intervention to direct complex biological processes (beyond conventional treatments for disease). It may also express concerns that science and technologies such as genome editing are moving too quickly for processes of critical reflection (e.g. law, regulation, cultural practices) to keep pace.

Moral norms and human rights

Concerns that certain uses of a technology may interfere with human rights are often invoked as reasons for ruling certain uses of a technology such as genome editing morally out-of-bounds. They may, equally, offer grounds for resisting the interference by the state or by others in the use of genome editing where there is no legitimate reason for doing so.

Welfare and risk

The concept of welfare suggests a potentially measurable set of consequences by which to judge and compare different proposed initiatives. The likelihood and nature of the expected benefits of genome editing, the possible harms it may lead to, and the risks associated with not doing it, may all figure in welfare calculations. Where the possible consequences of an action may lead to serious and irreversible harm, a precautionary approach may be favoured.

Social justice

The benefits and harms of genome editing, as with other technologies and innovations, are not necessarily distributed equitably between all people. Factors such as wealth, gender, sexuality, ethnicity, disability, class, and where people live may contribute to them being disproportionately affected by how genome editing is used. It may be appropriate to give special consideration to possible negative effects that could cause discrimination, injustice or disadvantage in society.

Governance and democracy

Many people are anxious to have clear limits that distinguish between morally acceptable and unacceptable uses of genome editing. A wide range of perspectives and values are likely to affect different people's judgment of the issues. Democratic procedures that take account of the range of views will have an important role to play in developing regulatory and practical ways forward.

We conclude…

When we think about how genome editing should be used, it is important to also think about how it should be governed. Given the public interest in the use of genome editing, an approach will need to be found that acknowledges that people arrive at these questions with different values, priorities and expectations.

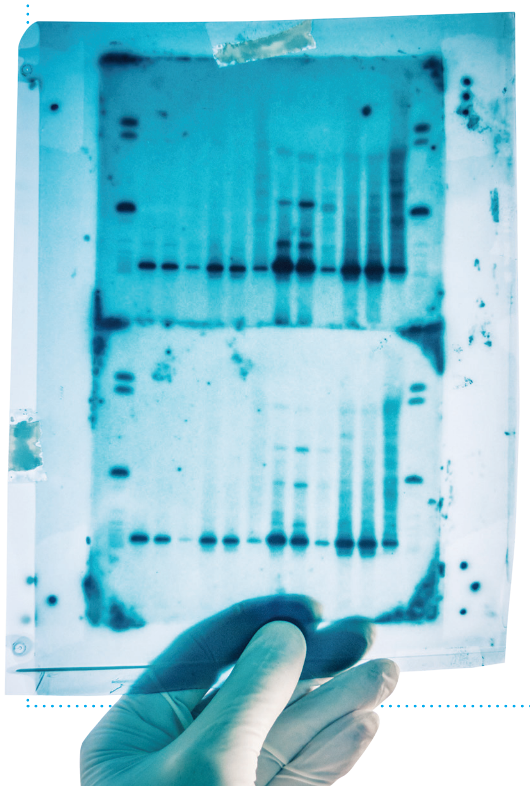
For more information please see **Section 3: Moral perspectives**

Human health

Genome editing techniques are now widely used in research across many areas of human health. In this section we look at basic research, and the prospects for treating disease, avoiding genetic diseases, and human enhancement. We explore the extent to which this raises new and distinctive ethical questions, and offers new perspectives on questions that have been discussed in the past.

Understanding human health through research

Health research often involves the use of animal models, such as mice, to investigate the causes of human disease and to study biological processes such as embryo development. Genome editing tools have enabled research techniques such as gene 'knockout' (deleting a gene to study its function in living organisms) to proceed more quickly, cheaply, and with greater precision. It has also made it easier to alter or insert DNA sequences, and to make several alterations at the same time.



Ethical considerations

Ethically significant research possibilities raised by genome editing include:

- Bringing basic research and its translation into treatment closer together, since alteration of a gene could serve both to discover its function and to enable treatment of a disease caused by that gene.
- A potential increase in the use of larger animals, such as primates, in disease research, as they may offer better 'models' for studying certain diseases.
- Using genetically altered animals to study the effects of gene mutations that are specific to a family or individual, introducing a direct connection between an animal model and an individual patient.

Potentially increased rates of experimentation, facilitated by genome editing, may prompt a number of additional concerns for some people, including:

- The possible consequences of an increased demand for the use of human embryos for research involving genome editing.
- The risk of scientific publishing and communication moving too slowly to keep pace with experimentation, meaning a lack of coordination among research groups and duplication of work, which may in turn have consequences such as unnecessary increases in the number of animals used in research.

Treating disease

Genome editing might have a transformative impact in many areas of medicine. Three areas in particular are:

- **Cell-based therapies,** e.g. transplanting genome-edited white blood cells into patients to attack HIV infection or blood cancers such as leukaemia and lymphoma.
- **Gene therapy,** e.g. to correct mutations that cause genetic diseases in particular tissues or organs, such as muscular dystrophy.
- **Xenotransplantation** (transplantation of organs from one species to another), e.g. from pigs to humans, where the pig cells have been altered to prevent the transmission of viruses.

Ethical considerations

As with any new treatment, there will be questions over the safety of the technique, whether it is likely to work, and whether it should be offered as an alternative or replacement for current treatment options. The main safety consideration with genome editing in patients is the possibility of unintended effects due to off-target DNA alterations. Given concerns over the uncertainty of outcomes, a relevant consideration will be whether alterations to the genome in patients' tissues can be neutralised or reversed.

Avoiding genetic disease

There are more than 4,000 known, inherited, single-gene conditions, which, collectively, are thought to affect at least one per cent of the world's population. The use of genome editing in reproductive treatments could prevent the transmission of some of these conditions (e.g. thalassaemia or cystic fibrosis) to future generations, by making changes to the DNA of a very early stage embryo that will be replicated in all cells in the body as it grows.

Ethical considerations

Genome editing may offer an alternative approach to familial disease prevention, especially in certain (albeit rare) cases where established methods such as pre-implantation genetic diagnosis (PGD) would not be effective. Many people have concerns about the possible use of genome editing in human reproduction, for example, about the implications of making genetic changes that will be passed on to future generations. Whether it is offered as an 'alternative' reproductive treatment depends not only on the outcomes, risks, costs, etc., but also on other factors including how reproductive choice is valued, and the extent of society's interest in people's choices and welfare, which may, in turn, have consequences for governance and regulation.

Human enhancement

Genetic variations may not always directly cause disease, but may be associated with an increased risk of developing a certain disease or, conversely, have a protective effect against a certain disease. For example, a recent laboratory trial of genome editing of preimplantation human embryos reported the introduction of a gene variant offering protection against HIV.

Genome editing also raises the possibility of 'engineering' humans with desirable genetic traits, for example to suit specific environmental conditions or to enhance athletic ability.

Ethical considerations

A much discussed issue is how to distinguish between acceptable and unacceptable uses of genome editing.

There are concerns that the use of genome editing may facilitate the spread of 'consumer' or 'liberal' eugenics, driven primarily by the choices of parents, which could, in turn, exacerbate divisions or inequalities in society. Some people may also be ethically opposed to the practice of pre-determining a person's genetic characteristics, arguing that this constrains their future choices in unacceptable ways.

For more information please see Section 4: Human health

Food production

Genome editing could help contribute to a sustainable increase in worldwide food production by improving the efficiency of the development and production of crops and animals for consumption.

Plants

Genome editing is currently used in research into plant breeding. Possible commercial uses include improvements in yield and pest resistance, increased drought tolerance, and increased nutritional benefit.

The impact of genome editing techniques is perhaps less revolutionary in plants than in humans, given the already long history of breeding strategies that have changed the genetic characteristics of virtually all crops – including selective breeding and first generation 'genetically modified' plants (mainly involving the insertion of genes that do not naturally occur in those plants).

However, genome editing could significantly speed up the progress of breeding programmes. It is thought that genome editing could reduce the time needed to generate the desired genetic characteristics in a plant population from 7-25 years to as few as 2-3 years since its target specificity effectively bypasses the need to go through a number of plant generations to achieve a particular genetic combination.

Depending on the regulatory and economic conditions, it could open up the field to smaller companies and, potentially, drive the development of characteristics other than the main commercially important traits like herbicide resistance.

Animals

Genome editing in animals has not merely accelerated research but has made possible research that was previously unfeasible. Recently the CRISPR-Cas9 system has been proposed for use in pigs, sheep, cattle, and chickens:

- to improve yield – e.g. chickens that produce only female offspring for egg production;
- to increase disease resistance, e.g. pigs that are resistant to African swine fever; and
- to make livestock better adapted to farming or environmental conditions, e.g. hornless cattle that can be kept in confined spaces with lower risks of injury.

Three principal challenges in genome editing of livestock are scaling up the technology to commercially viable levels, securing regulatory approval, and farmer and public acceptance.

Ethical considerations

Global food production needs to increase – some say by as much as 70 per cent – to support the world's growing population. It is important to look at the big picture of food production, and to consider whether and how genome editing technologies can contribute alongside other approaches such as improving the efficiency of distribution and reducing waste.

The safety of food for human consumption is a key concern and, in the case of animals, there are also concerns about the welfare of intensively farmed animals.

One area of dispute is whether foods produced using genome editing techniques should be classed as genetically modified (GM). This is significant because of the differences in the way that GM and non-GM foods are regulated, labelled and perceived by consumers.

GM regulation imposes additional burdens on producers, which affect the economics of production. Effective regulation and labelling depend on traceability but genome editing makes analytical verification of this difficult, as an edited product may appear to all intents and purposes identical to a non-edited product. Whereas appropriate labelling of foods enables consumers to exercise a greater choice about what they buy, it is important to consider what may be implied in and inferred from product descriptions, and what is the appropriate information to give to consumers.

For more information please see **Section 5: Food**

Wildlife and ecosystems

Some applications of genome editing include the creation and release of genetically altered species into the wild, with the aim of deliberately affecting an existing ecosystem.

What is a 'gene drive'?

Wild species tend to adapt to their conditions through a process of natural selection, whereby a genetic trait that appears spontaneously aids survival and reproduction in the wild and spreads throughout a population over successive generations.

Researchers have recently discovered a way to ensure that a selected genetic variant is preferentially inherited using a technique called a gene drive. The aim is that the genetic variant spreads through a population regardless of whether or not it improves the chances of survival of members with that variant. Gene drives are likely to be of most use in species with short reproductive cycles such as insects; however, they are not infallible as they are themselves subject to spontaneous mutations and may be out-competed in the wild.

Gene drive systems that make use of CRISPR-Cas9 have been described as a potential 'game changer' in manipulating wild insect populations due to their ability to make certain precise changes to DNA sequences to give controllable effects.

Potential applications include:

- **Infectious disease control:** in insects, such as mosquito species that transmit malaria, dengue fever and the Zika virus, the aim is to disrupt essential genes which are involved either in reproduction, so as to reduce, or ultimately to eradicate the species, or that give them the ability to carry and transmit the disease.
- **Controlling predator populations:** genome editing techniques could also potentially be used to eliminate predators and pests to help to restore threatened native species of animals and plants.
- **Reintroduction of extinct species:** a more speculative use of genome editing might allow biologists to 'resurrect' extinct species such as the passenger pigeon and reintroduce them to their previous habitats.

Ethical considerations

There are potentially significant public health benefits arising from the use of gene drives that make use of genome editing techniques. For example, its ease of use and relative efficiency offer the potential to transform a mosquito population at lower cost and over a shorter time, which could be very significant for resource-poor regions, for example where malaria is most prevalent (around 90 per cent of all deaths from malaria occur in Burkina Faso, Mali and Uganda). There are, similarly, economic benefits to cost-effective pest control in agricultural regions.

However, the potential risks of uncontrolled proliferation of gene drives in the wild are of concern, particularly as the impact of the drive on the ecosystem may be unpredictable and irreversible. There are fears about unexpected or unintended consequences given that ecological systems are difficult to predict or control, and the possibility of gene drives being put to malicious uses, for example to intentionally cause an ecological catastrophe.

The deployment of technologically advanced gene drives and genome editing systems in resource-poor countries also raises questions about appropriate conditions of technology transfer. The values and priorities of recipient communities are important considerations and cannot simply be assumed – they will depend on many factors, and efforts must be made to engage with the range of expectations of the communities who will be most affected.

We conclude…

The introduction of gene drives into the wild should be approached with caution. It requires flexible and adaptive methods of governance that involve built-in opportunities for break points, and reflection and ongoing appraisal of the technologies in relation to other possible solutions to a problem, taking into account the values and priorities of those directly affected.

For more information please see Section 6: The natural environment

Other applications:

industrial, military and amateur use

Microorganisms are more amenable to genetic modification than plants, animals and humans. Genome editing techniques (themselves derived from defence mechanisms in bacteria) provide new tools for modifying bacteria to achieve production of fuel, chemicals and proteins for a variety of uses.

Industrial applications

Industrial applications of genome editing in bacteria include the production of fossil fuel alternatives, food additives and flavourings, antibiotics, herbicides and vaccine production. Potential benefits of this method of production include fast turn-around times and the use of cheap supply materials (even waste products in some cases).

Amateur applications

The comparatively low cost, ease of use and availability of online kits making use of genome editing technologies mean they are accessible to amateur users outside of regulated industrial and academic environments. These may include DIY ‘garage’ scientists, school and undergraduate students (e.g. in biology competitions), and others with an interest in biological research and the possibilities – whether potentially beneficial or harmful – raised by genome editing.

Ethical considerations: biosafety

Genome-edited organisms (as with all genetically modified organisms or GMOs) pose a possible risk of harm to those handling them, and to others or to natural ecosystems if they are released or escape from controlled environments.

Most countries have layers of regulation which cover the handling, transport and release of GMOs, but there are concerns about how these can be managed outside of regulated environments, for example in countries with less well-developed structures, and by individuals who are not disciplined with regard to health and safety procedures.

Military applications

Military interest in the applications of genome editing may be focussed on its potential for defence purposes, for example to counteract the release of a harmful substance to a population.

There is also speculative interest in the possibility that genome editing may one day have a role to play in the selecting or enhancing of military personnel in relation to genetic susceptibility to disease or improved physical fitness.

Ethical considerations: dual-use

Research that has both civilian uses and a significant potential for military (or terrorist) use is known as ‘dual use research of concern’. The possibility of genome editing being put to harmful uses, for example in the production of bacteria intended to cause disease outbreak, is recognised by many countries as a threat to national security.

Controls on access to certain materials, and policies for monitoring and recording research, aim to address this, but it may be the case that these sorts of measures need to be enhanced, particularly because suppliers of genome editing kits and materials are not currently required to carry out any checks on the people who purchase their products.

For more information please see **Section 2: Science in context**

Conclusions

Genome editing is having a transformative effect in many areas of biological research. It is being taken up widely and has spread quickly due to the advantages it offers to those using it: it is affordable and easy to use; it gives faster results; it is efficient at making precise edits to DNA; and it offers the prospect of making these edits at multiple sites in the genome in a single procedure.

This review has identified some of the key issues and questions that may arise in relation to potential future uses of genome editing in treatments and technologies that could be applied in humans, animals, plants, and microorganisms. The ethical questions are very different, depending on the context of application. In view of this, we believe that focussing primarily on the ethical implications of the technology itself is not the best way to approach further appraisal of the ethical and social issues. Instead, we propose a second stage of work that starts by looking critically at problems or challenges that genome editing may contribute to addressing, and offer an ethical analysis of the ways of approaching them in which genome editing may play a role.

Next steps: what are the priorities?

The review has identified two priority areas which require urgent ethical consideration: human reproduction, and livestock. Accordingly, the Council will now set up two expert Working Parties to develop practical conclusions and recommendations in response to the issues and questions raised in this initial stage of the project. Their findings and recommendations will be reported in 2017.

The box on the following page highlights further issues identified in the review that we believe need to be addressed in the near future, and issues that need to be kept under review.

Issues that should be addressed urgently

Human reproduction

Why?

Of all the potential applications of genome editing that have been discussed, the one that has consistently generated most controversy is the genetic alteration of human embryos in vitro. Research undoubtedly has a very long way to go before any application of this sort could be contemplated and, in the UK at least, the transfer of an edited embryo to a woman is currently prohibited by law. Nevertheless, such applications are theoretically possible and there are strong moral arguments for them, at least for limited purposes, as well as against. The principal challenges are the very difficult questions of what would be required to demonstrate safety and efficacy, and of resolving the ethical arguments for and against attempting it. It is therefore appropriate to consider carefully how to respond to this possibility before it becomes a practical choice.

Addressing these difficult questions now will help to meet concerns that technology is rushing ahead of public debate and allow such debate to influence the development of the technology, distinguish acceptable from unacceptable aims, and reduce the uncertainty and ambiguity for researchers and potential recipients of the technology.

Livestock

Why?

Genome editing offers a potential contribution to the challenge of maintaining a sufficient supply of safe, nutritious food. Research in this area is comparatively well advanced, but has received little attention compared to other uses of genome technologies.

There are important questions to consider regarding the appropriateness of existing regulations and whether there is a need for new classifications or new approaches to policy and regulation. The answers to these questions could have important consequences for food security, businesses, international trade and the economics of food production.

Issues that may need to be addressed in the near future

- The use of CRISPR-Cas9-enabled gene drive systems in wild species to prevent infectious disease transmission.
- The use of genome editing to make animal tissues and cells suitable for transplantation to humans (xenotransplantation).

Issues that should be kept under review

- Genome editing to develop new cell-based therapies for existing diseases.
- The use of genome editing to develop new plant strains in agriculture.
- Changing patterns of technology use, including military and national security initiatives, artistic and cultural activities, and private experiments by community groups or individuals.

Overview

Recent advances in genome editing such as the CRISPR-Cas9 system are transforming many areas of biological research and have the potential to change our expectations and ambitions about human control over the biological world.

The possible effects of such advances raise important ethical questions across many potential areas of application of genome editing, for example in:

- Human health
- Food
- Wildlife and ecosystems
- Industrial, military and amateur uses

In this first stage of our work, we have concluded that there is a need for urgent ethical review in two areas of potential application: human genome editing for the avoidance of genetic disease; and genome editing in livestock to improve systems of animal husbandry and food production.

The Council will now begin work on two further inquiries which will address ethical and practical questions and make recommendations relating to the possible uses of genome editing in these two fields.

Other areas, including gene drives to control mosquito populations that spread infections disease, will also need further ethical consideration in the near future.

This guide and the full review are available on the Council's website: **www.nuffieldbioethics.org**

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