Section 8

Conclusions

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Outline

The difficulty of predicting how technological innovations are likely to develop is noted and the approach taken in the report is reviewed.

The features of genome editing, in particular the CRISPR-Cas9 system, that give rise to significant ethical questions are reviewed, including the novelty of the mode of action, accessibility (including low cost and level of knowledge and resourcing required), speed of use from design to results and of uptake across life science sectors, and potential to achieve multiple simultaneous edits.

The role of ethical reflection with regard to different applications of genome editing is proposed: three sorts of inquiry are recommended.

Societal and moral issues identified in the report for further consideration are divided into those that should be addressed urgently, those that may fall to be addressed in the near future and those that should be kept under review.

8.1 This review has confirmed the impression of rapid uptake and diffusion of genome editing across many fields of biological research. This spread is overwhelmingly attributable to the CRISPR-Cas9 system, although that technique is itself still undergoing refinement. Indeed, new technologies may emerge that could affect genome editing with even greater precision and speed. There are, nevertheless, variations in the purpose and pattern of use between different fields of research. Although the impact of genome editing in research is already impressive many of the issues we have identified anticipate the potential future uses of genome editing as a core component of many new treatments and technologies. Predicting the future of technological developments is notoriously difficult. At a gross level, a number of common tropes warn of the potential errors of both over-expecting and under-anticipating the impact of new technologies.[511] This difficulty applies not only to the timescale according to which productive applications emerge, but also the directions that technological development may take. It should be remembered that most prospective technologies fail, and that some lead to undesirable consequences, a fact often obscured by 'whig' histories that reconstruct the history of successful technologies and their beneficial social consequences. Scientific discovery and technological innovation is important but not inevitable. Most important among the factors shaping technological development is human agency. It is human agency, in terms of decisions that are made about directions of research, funding and investment, the setting of legal limits and regulatory principles, the design of institutions and programmes, and the desire for or acceptance of different possible states of affairs, that will determine whether, and which, prospective technologies emerge and, ultimately, their historical significance.

8.2 In this review our approach has been analytic: we have looked into the technology of genome editing, isolated aspects of it and examined the part it may play in different settings. From the beginning, however, we have anticipated a second phase of our work, in which we will develop normative conclusions, advice and recommendations. The starting point for this work will not be the technology itself but rather one or more fields of activity, 'challenges' or 'problems' in which genome editing emerges and on which it is having or is expected to have an impact.

[511] The so-called 'First law of technology', usually attributed to US scientist and futurologist Roy Amara, states that the impact of technology tends to be overestimated in the short term and underestimated in the long term. The Gartner consultancy's widely-cited 'hype curve' suggests that initial over-excitement about technology usually leads to disillusionment followed by gradual productivity gains. These have in common with the 'productivity paradox' (famously noted by the economist Robert Solow with reference to electronic computing technology) the suggestion that delayed productivity may be less about the intrinsic features of the technology than about its embedding within, and transformation of, systems of production and associated conditions. In *The shock of the old*, the historian of technology David Edgerton warns against neophilia distorting judgements about the overall social importance of different technologies. See: Edgerton D (2008) *The shock of the old: technology and global history since 1900* (London: Profile Books).

What is ethically challenging about genome editing?

8.3 A number of features of genome editing, especially CRISPR-Cas9 and analogues, have emerged from our inquiry as sources of issues that require further ethical consideration:

- **Novel mode of action.** In a research context genome editing is demonstrably effective at making small, precise and specific edits to DNA in living cells. This means that it can be used to 'knock out' genes or to change their function by adding or replacing sections of DNA. It is a significant feature of the CRISPR-Cas9 technique that these 'edits' need not leave any tell-tale trace of their origin in the genome, in the sense that subsequent genome analysis is able to tell whether they have been introduced intentionally or arisen through common or garden random mutation. Variations of the technique, currently being developed, could achieve similar effects at the epigenomic level. These features challenge distinctions (like that between GMOs and non-GMOs) on which important aspects of normative systems, like the system of food regulation in the EU, are based. The ambiguity produced by genome editing challenges us to think about what is significant about such distinctions and to review our moral attitudes and practical measures accordingly.[512] Similarly, the theoretical possibility of changing a disease-causing point mutation in the genome of an early human embryo into a common, non-disease causing variant, without any other alteration, challenges us to reconsider the reasons for existing prohibitions on deliberately causing genomic alterations that may be inherited by future generations. Finally, the significance of epigenome alterations as opposed to genome alterations, or alterations of other kinds in biological systems, and how these fit with existing norms, would benefit from greater attention in the context of what CRISPR-Cas9 might achieve.

- **Accessibility.** Compared to previous techniques for genetic manipulation, and to previous editing systems, CRISPR-Cas9 and its analogues are comparatively affordable and easy to use. The fall in cost of genome manipulation can be compared to that of semiconductor technologies and genome sequencing. But it is especially as a technology *converging with* semiconductor and genome sequencing technologies, and other technologies that are also rapidly descending in cost and increasing in power, that genome editing holds genuinely transformative potential. The incorporation of genome editing into proprietary technologies and kits that are both affordable and approachable by a greater number of users, including users outside élite communities and institutional settings, challenges us to think about how ethical reflection and governance systems can engage effectively with technology use (if not through élite communities, institutions, learned and professional bodies, traditional businesses, etc.). Similarly, the range of interests potentially engaged by the directions in which genome editing technologies may develop represents a challenge to the principles of scientific and commercial freedom, and to political procedures for discovering and asserting the public interest (including the protection of potentially disadvantaged groups).

- **Speed of use and uptake.** Closely related to the cost and ease of use, the increased speed with which genome editing allows genetic manipulation to be achieved (within the context of a research project, for example) and the speed of its uptake and diffusion among use contexts may exacerbate uncertainties or ambiguities that exist in applying governance systems and existing norms. This speed and diffusion makes what might have been a difficult but limited and local problem into a widespread and highly consequential one. In many cases (as with the governance of medical and reproductive innovations in the UK) there may be existing provisions that are be both applicable and robust. They may not, however, be optimal (for example, given the novelty of the mode of action discussed above). Optimising them is important because there are ethical considerations on both sides (for example, in favour of both liberalising and of constraining the use of the technology; it is not simply that technology

[512] While these distinctions may *appear to be questions of fact susceptible of straightforward answers, we hold that the answers to such questions in fact are complex amalgams of factual and moral judgements* or the result of political compromise. (The italicised words are taken from the Report of the Committee of Inquiry into Human Reproduction & Embryology (the 'Warnock Report') 1984 (Cmnd 9314) (London: HMSO).

moves inexorably in one direction and ethics restrains it). Speed of innovation may perturb the balance between these considerations. Differences in the speed of development of research and innovation compared to the pace of development of related systems, including normative systems (for example, changes to the law, to institutional structures, regulatory policies and procedures, and the evolution of public moral consensus) can, likewise, exacerbate conceptual inconsistencies, increase anxiety and give rise to distrust. Such differences call for new terms of reconciliation between biomedicine and biotechnology and society. In an open society the establishment of these terms requires effective social processes, which may be hampered by restrictions on the flow of information, or the inconsistent assignment of social meaning.[513] A further source of concern is that speed of diffusion may cause technology to become prematurely locked in, before the implications have been explored and evaluated adequately, or before related systems needed to optimise it are able to catch up.[514] (We heard in evidence how it is difficult to get papers published and obtain grants in certain fields without genome editing as part of the methodology; this suggests a potential, at least, for genome editing to crowd out other research, or change the deployment of research resources such as laboratories and staff, or even change the aims of research to those that are more amenable to genome editing.)

- **Multiplexing.** A final reason for further ethical reflection on genome editing is the potential to achieve multiple edits in a given genome. This could revive the prospects of techniques such as xenotransplantation, by overcoming limitations that have constrained them in the past. Although xenotransplantation has been discussed at length, genome editing may constitute a significant change in the context of these debates.[515] Multiple, simultaneous (multiplex) editing, or multiple rounds of editing in successive cell lines (followed by nuclear transfer cloning techniques or direct reprogramming of cells to gametes), could, additively, achieve large-scale genetic alterations, potentially creating synthetic genes or transgene analogues, or developing complex synthetic organisms or organic components. In this respect it is a potentially significant enabler of future synthetic biology and a potential disruptor of established species classifications.

What role should ethical reflection play?

8.4 The focus on the technology tends to obscure rather than reveal the social and ethical issues. It also masks questions that arise at different spatio-temporal scales.[516] (Earlier, we noted the potentially misleading use of 'precision' when talking about genome editing, given that the functional outcomes at the level of the organism in its environment are not precisely prescribed, or may be so only in exceptional cases). Advances in knowledge about which target sequences have a predictable phenotypic effect when altered and methods of delivering the genome editing machinery into living cells at high efficiency are, potentially, at least as significant as the discovery

[513] Popper K (1945) *The open society and its enemies* (London: Routledge).

[514] "By the end of 2014, CRISPR had been mentioned in more than 600 research publications. [This figure has, as of June 2016, more than doubled.] "[…] in terms of shaping research and development, resources for cataloguing the vast quantities of data CRIPSR generates are sorely needed to encourage and facilitate collaboration and knowledge sharing. One such rare resource is CrisprGE: a dedicated repository-containing total of 4680 genes edited by CRISPR/Cas approach (Kaur et al., 2015). Allocations of realistic funding in all areas across this field are essential to achieve this." Response to Call for Evidence by Dr Helen O'Neill.

[515] Xenotransplantation was discussed extensively in the final decade of the last century (e.g. Nuffield Council on Bioethics (1996) *Animal-to-human transplants: the ethics of xenotransplantation*, available at: http://nuffieldbioethics.org/project/xenotransplantation/). In 1997, a regulatory authority, the United Kingdom Xenotransplantation Interim Regulatory Authority (UKXIRA), was established in anticipation of imminent medical treatments. But the technique foundered on a number of technical hurdles. UKXIRA was disbanded in 2006. See: McLean S and Williamson L (2007) The demise of UKXIRA and the regulation of solid-organ xenotransplantation in the UK *Journal of Medical Ethics* **33**(7): 373-5.

[516] Some of the discussion of genome editing implies or, at least, does nothing to counteract the impression of lingering genetic determinism: the belief that genotype strongly determines phenotype. This impression may be partly a hermeneutic phenomenon: a consequence of inattention to context, for example taking scientific papers out of their implicit frame of reference. But this does not diminish the importance of careful communication and translation of ideas between audiences and discourses.

of effective genome editing techniques and will not necessarily be deliverable in every desired case (or, indeed, in most, or even in many cases).

8.5 We are convinced that it makes little sense to treat the questions raised by genome editing as if they belonged to a single field (a hypothetical discipline of 'genome editing studies').[517] Rather, they should be addressed as part of different technology convergences (e.g. with ART, with gene drives, with agricultural technologies, etc.), which also includes political technologies (regulation, legislation, etc.). But, more than that, we conclude that it is not the scale at which questions are posed but also their orientation that is important. Beginning with questions about what can be achieved at the genome level risks reducing all questions to 'ELSI' questions (questions about the ethical, legal and social implications of genome editing, as if that were the only or most obvious pathway available to address a complex set of real world challenges) and leaving questions about the appropriateness of genome technologies in any given case unaddressed. This is why the next, normative, phase of our work should begin with problems or challenges (and the potential diverse framings of those challenges), rather than technologies, and adopt a comparative methodology.

8.6 In the light of the inquiry to date, we conclude and recommend that this second stage of work should involve at least three elements:

- an account of the value commitments that are at stake in the distinctions that are made in existing governance arrangements that are effective in the area under consideration (and in any proposals to revise these);
- an identification of where public and private interests are mutually engaged, and the legitimate force of these (i.e. who is entitled to determine what may or should be done?);
- a comparison of the different visions of desirable future states of affairs and narratives about technological and social developments, which continually re-imagine possible outcomes, feeding back into a public discourse informing governance.

Triage of issues for ethical consideration

8.7 We divide the issues that we have identified in our inquiry to date into three categories: those that should be addressed urgently, those that may need to be addressed in the near future, and those that should be kept under review. Because, as we have argued, the questions should be situated within a particular sociotechnological context (a historically and geographically defined site where social and technological conditions interact) the questions are elaborated below in relation to prospective uses of genome editing and that, therefore, define a proposed programme of further work.

Issues that should be addressed urgently

Human reproduction

8.8 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* and the possibility that altered embryos could be transferred to a woman who would give birth to a human being with a unique, altered genome. In identifying this as a question that should be urgently addressed we do not mean to imply that such a birth is imminent.[518] The safety and efficacy of the genome editing technique has not been demonstrated sufficiently through research in human embryos and, in the UK at least, it would be a criminal offence to transfer an edited

[517] The analogy to nanotechnologies, suggested by a respondent to our *Call for Evidence*, is apt here: see response by Donald Bruce.

[518] Controversialists have, nevertheless, predicted that such a child will be born somewhere in the world within the next couple of years or has already been born.

embryo to a woman unless the law were to change to make it permissible, a process that would undoubtedly take a number of years, even if the wheels were to be set in motion without delay.

8.9 The reasons for considering this urgently are therefore not because the applications are imminent, but because the path, if it is to be embarked upon, will be a long one, and will be made longer if departure is delayed. Deciding whether it should be broached *at all* is therefore both pressing and ethically highly complex, and therefore likely to be difficult to resolve. But if the conclusion of this process is that applications of this sort should be permitted, it is better that they should be available as soon as possible. (The moral arguments in favour include the alleviation of human suffering and prolonging implementation would, all other things being equal, extend this suffering.)[519] It is also preferable for ethical reflection to shape the course taken rather than to appear as a final hurdle to 'overcome' when the research has already been accomplished, resources committed, and hopes and fears piqued. Such reflection can also help to mitigate the risk of path dependency and ensure that alternative avenues of research continue to be considered. Addressing this issue now will help to meet concerns that research and technology development 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 under which researchers and potential beneficiaries live. Furthermore, the strength and unreconciled diversity of public opinion in this area cannot be denied and constitute, in themselves, good reasons for engaging with it.

8.10 Research undoubtedly has a very long way to go before any application of this sort could be contemplated. But whereas therapeutic applications of genome editing to address existing disease states face challenges in terms of delivery and achieving efficiency *in vivo*, altering a point mutation (or a small deletion) in a human embryo without harming the embryo's development is potentially a closer prospect based on research in model organisms. We already stand to learn much about the use of genome editing in human embryos from research that has recently been approved by the HFEA.[520] The principal challenges in this case are the very difficult questions of what would be required to demonstrate safety and efficacy, and resolving the ethical arguments for and against attempting it.[521] It is, furthermore, an issue that the Council is well placed to take up, following from the observation at the end of our 2012 report *Novel techniques for the prevention of mitochondrial DNA disorders: an ethical review* that:

> "the wider policy debate could benefit from a fuller discussion of the ethics of different kinds of prospective and theoretical germline therapies. This would include potential therapies that would act on the cell nucleus with heritable effects, and therapies which might involve nuclear transfer in its various forms. The ethical robustness and sustainability of policy decisions made around cell reconstructive therapies and other potential treatments for serious genetic disorders would benefit from a thorough discussion of the full range of these other prospective treatments."[522]

8.11 Despite the amount of consideration that these questions have received the controversy remains unresolved. We do not believe, however, that this is the result of an intractable opposition of principled positions, but of complex judgments made in a changing context of relevant factors. Many features of this context have changed since current policy positions were established, even since 2012, the development of genome editing technologies not the least of them.

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[519] In this respect the arguments are analogous to successful arguments for permitting research on human embryos that would lead to the development of stem cell therapies – the sooner the research is achieved, the sooner the therapies might be available, and affected people could be treated.

[520] See http://www.hfea.gov.uk/10187.html.

[521] Although raising distinct issues in many respects, relevant consideration of what is required to demonstrate sufficient levels of safety and efficacy for translation into clinical use is currently being undertaken in the UK in relation to cell reconstruction techniques for the avoidance of mitochondrial disorders (so-called mitochondrial donation).

[522] Nuffield Council on Bioethics (2012) *Novel techniques for the prevention of mitochondrial DNA disorders: an ethical review*, available at: http://nuffieldbioethics.org/project/mitochondrial-dna-disorders/.

Livestock

8.12 Genome editing offers a potential set of responses to the challenge of developing and maintaining a sufficient supply of safe, nutritious food. As we observed in the section on food, research on the genetic alteration of livestock is comparatively well advanced, and some of the threats to current systems of husbandry (such as livestock diseases) that it may be used to address are well understood. These two factors make this a significant topic. There is, furthermore, considerable difference of moral opinion about the appropriate role of different foods and husbandry methods in relation to the overall challenge of food security. At the most general level, there are debates about the relative contributions of animal and vegetable resources to the food supply. All these debates are potentially affected and possibly exacerbated by changes in the relative efficiencies of different food production methods that might be brought about by genome editing.

8.13 Given its imminence, and in contrast to the very considerable public debate that has surrounded genetically modified crops, comparatively little attention has been given to genetic livestock manipulation and its regulation (at least where the animals concerned may not be regarded as 'genetically modified organisms' as defined in relevant legal instruments). Much attention has, however, been given to alternative methods of husbandry and the role of livestock of different kinds in meeting people's needs and desires for food. Genome editing may play a potentially significant, though morally ambiguous, role in relation to sustainability, intensity, yield, human and animal welfare and quality.

8.14 Particularly strong feelings are aroused by issues surrounding animal welfare. It is possible, though certainly not obvious, that genome editing could have direct effects on animal welfare. More likely, it could have indirect effects by making feasible different regimes for raising animals. Cattle genomically modified to lack horns, for instance, might potentially be kept in denser populations than would otherwise be possible. A reasonable debate on these issues is likely to be fostered by careful attention to as wide as possible a range of ways in which genome editing might affect animal welfare.

8.15 As with human applications, questions arise about the appropriateness of existing regulatory distinctions and the complex reasons, some of them ethical reasons, that underlie them. It is appropriate to ask, therefore, whether there is a need for new classifications or new approaches to policy and regulation. Also, as in the case of human applications, questions arise about the nature and force of the public interest, how this may affect commercial freedoms and welfare considerations, and what the appropriate scope and modalities of regulation should be. The answers to these questions will have important consequences for businesses, international trade, and the economics of food production.

Questions that may need to be addressed in the near future

Editing of wild animal species to prevent disease transmission

8.16 The use of gene drive technology has already been noted as raising significant public ethical issues and has been the subject of inquiries by major national bodies.[523] The combination of gene drives with genome editing technology potentially raises additional issues by enabling previously intractable obstacles to be overcome and therefore, a greater number of aims to be pursued. The most significant of these, currently, is the alteration of mosquitoes to prevent the transmission of tropical diseases. There are very significant concerns about the ecological risks of releasing gene

[523] National Academies of Sciences, Engineering, and Medicine (2016) *Gene drives on the horizon: advancing science, navigating uncertainty, and aligning research with public values* (Washington, DC: The National Academies Press), available at: http://www.nap.edu/catalog/23405/gene-drives-on-the-horizon-advancing-science-navigating-uncertainty-and; House of Lords Science and Technology Select Committee in its report *Genetically modified insects* (2015), available at: http://www.publications.parliament.uk/pa/ld201516/ldselect/ldsctech/68/68.pdf.

drives into wild populations although the likelihood of these risks materialising is a matter of scientific disagreement.

8.17 There are, however, established international regulatory pathways for release of GM mosquitoes, which mean that environmental release would have to take place in a controlled and staged manner, through successive trials, which entail a significant cost burden for developers. Key considerations must be robustness, reversibility and control: whether an intervention is able to retain structure and efficacy while adapting readily to major environmental change and/or other major challenges, whether it is reversible and whether it is local or systemic. From the current stage of development of genome editing-enabled gene drives, large-scale release is likely to be at least a decade away. However, this does not mean that ethical examination is currently not required. There is much work to do to ensure that, at the very least, development of the technologies in any geographical area takes proper account of the values, priorities and preferences of the communities affected.

Xenotransplantation and humanised animals

8.18 As noted above, the potential capacity of genome editing to overcome bottlenecks in xenotransplantation research, for example, in terms of reducing the risk of zoonosis (the transmission of viruses between animals and humans), or in terms of addressing adverse immune response suggests that new routes to treatment of diseases requiring tissue or solid organ transplants may open up. Many of the ethical questions regarding xenotransplantation have been debated in the past although, as research progresses, these may need to be recalled for a new generation and the question of appropriate regulation may need to be revisited.

Questions that should be kept under review

Cell-based therapies

8.19 One of the most promising areas of development using genome editing is cell based therapies for existing diseases (discussed in section 4). These raise a number of difficult questions with regard to demonstrating safety and utility, and about when they should be introduced into clinical practice and applied to particular patients. We do not feel, however, that for the most part the issues raised are distinctively different for genome editing.

8.20 There exist clinical trials and approvals protocols for pharmaceuticals and medical devices that provide for these questions to be addressed. Partly because of these, therapies currently under development are likely to take some time yet to get into clinical practice. We have noted the tension between following these protocols and the imperative to get effective treatments to patients in serious need. And there has been some concern among researchers about the confusion between genome editing research on somatic cells and research on embryos. However, these do not appear to have a peculiar force in relation to genome editing or be incapable of being addressed in existing ways.

Plant science

8.21 We noted that genome editing is unlikely to have the same transformative impact in plant breeding as in other areas of biomedicine and biotechnology, at least without significant advances in other areas of knowledge and technical capability needed to produce predictable and stable phenotypes from genetically altered plants. It is likely that many new plant varieties produced with the use of genome editing may not be regarded as genetically modified organisms (GMOs). Others may, however, be regarded as GMOs. How that distinction is drawn will be potentially significant, given the regulatory burden that the GMO classification places on producers. This classification is, in any case, likely to be the site of a boundary dispute between biotechnology companies and civil society organisations with principled reservations about the use of genome technologies in food production. It may also have a significant effect on shaping the industry, including the new non-GMO biotechnology space, which might provide an entry point for a new wave of small and medium sized enterprises. It will be important that this is kept under review since it may have

implications for the direction or speed of development of a new generation of plant varieties with beneficial characteristics such as drought tolerance or increased nutritional benefits (see section 5).

Changing patterns of technology use

8.22 A larger and more amorphous set of questions arises from our consideration of genome editing outside the relatively well-defined spaces of biomedicine, agricultural biotechnology and public health. We noted that genome editing constitutes an important enabling technology for synthetic biology, and therefore for industrial biotechnology, and may have potentially beneficial applications in, for example, the production of high-value chemicals, materials and biofuels. (Whether they are publicly beneficial or not may depend largely on the economic conditions under which they are developed and introduced.)

8.23 While the private biotechnology sector is defined, if somewhat opaque, we noted that there are a number of even more opaque, less well-defined, or interstitial sites, outside the more-or-less transparently and more-or-less well governed spaces of recognised institutions, communities of experts and commercial firms. These include military and national security initiatives, artistic and cultural activities, and private experiments by community groups or individuals. Many of these are enabled by the accessibility of genome editing, noted above, and prompt questions about who 'owns' technology and their relationship with normative systems, if this is not through traditional professional or learned bodies, institutions, or communities. It suggests a need to consider the implications of an uncontrolled diffusion of powerful genome technologies, especially outside institutional settings. But it also indicates that applying normative systems only to traditional hierarchical social structures will increasingly overlook significant numbers of relevant actors and that new ways of engaging users of technology in moral communities may need to be found.

8.24 The likelihood of someone outside a well-resourced institutional or commercial setting accidentally (or deliberately, if they are a hostile non-state actor) generating a biohazard that presents a serious threat to themselves or the public may be remote currently, although this should be kept under careful review. It is welcome, in this context, that the scientific community and the national security agencies have, from their separate perspectives, responded prospectively to these possibilities.