

WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing

Background Paper ***The Ethics of Human Genome Editing***

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1 Introduction¹

The label ‘genome editing technologies’ commonly refers to technologies that allow scientists to make changes in the genetic sequences of organisms. Current genome editing technologies include zinc-finger nucleases (ZFNs), transcription activator-like effector-based nucleases (TALENs) and clustered regularly interspaced short palindromic repeats (CRISPR), with CRISPR-associated nucleases (Cas). CRISPR-based genome editing is considered more precise (it is possible to target specific sequences of DNA), more efficient (it has relatively few off-target effects) and cheaper to use than other genome editing technologies. As momentum builds around CRISPR’s experimental uses, a substantial debate has developed amongst scholars from a wide range of disciplines² (1, 2), national academies³, ethics bodies (3, 4)⁴, members of the public (5-7), learned societies⁵ (7, 8), and patients (9, 10). This debate concerns the ethical acceptability of its human applications, among others, and the mechanisms of governance that would be needed to regulate these applications.

CRISPR is an emerging biotechnology, and many view it as having a high level of disruptive potential for biomedical research and its associated ethical landscape (11-14). Disruption could occur by making previously inefficient procedures more efficient, by making hypothetical procedures possible, or by allowing new processes to be conceived of (15). The rapidity by which CRISPR has been adopted as an experimental technique in laboratories and as a gene transfer technology is partial evidence to some of this disruptive potential (13).

The present background paper provides an overview and an analysis of the ethical debate surrounding human applications of CRISPR genome editing and it is informed by a systematic search of the literature on the ethics of genome editing⁶. It seeks to present the range of views, assessments and arguments advanced within such ethical debate by scholars, and within grey literature (e.g. government reports and other policy-related documents). The background paper discusses key ethical questions, challenges and areas of controversy concerning human somatic genome editing and human germline genome editing. It then moves to survey proposals that have been advanced to construct mechanisms of governance for overseeing research with genome editing in humans.

Most debate about the ethics of genome editing has focused specifically on CRISPR, in part because of its prominence and disruptive potential. However, the boundaries of this debate as applied to a specific technology, CRISPR, are blurred. It is often unclear whether the issues discussed are

¹ The author wishes to thank the Committee’s members for their input on the background paper, and Dr Silvia Camporesi and Dr Robert D. J. Smith for detailed comments on earlier versions of the paper.

² This background papers incorporates key ethical arguments and views advanced within this debate by ethicists, scientists, social and political scientists among others.

³ Such as the US National Academies of Science, Engineering and Medicine; the European Society for Human Reproduction and Embryology and the European Society for Human Genetics, ESHRE-ESHG; the Federation of European Academies of Medicine, FEAM; the International Society of Stem Cell Research, ISSCR; the European Academies’ Science Advisory Council, EASAC; the American Society for Human Genetics, ASHG, among others.

⁴ Such as the Nuffield Council on Bioethics; the UNESCO International Bioethics Committee, IBC; the Deutsche Ethikrat; the European Group on Ethics in Science and New Technologies, EGE, among others.

⁵ Such as the Royal Society; the German academy of sciences; the Leopoldina; the French medical research institute; the Netherlands Commission on Genetic Modification, COGEM, among others.

⁶ Searches of abstracts, titles, keywords and text were performed in the databases Scopus, PubMed, Web of Science, JSTOR and PhilPapers using the following terms: ‘gene editing AND ethics’; ‘genome editing AND ethics’; ‘gene editing AND morality’; ‘genome editing AND morality’.

specific to CRISPR and therefore not applicable to other existing or future genome editing technologies. Hence, there is a need to adopt a broad gaze while also maintaining specificity, and for this reason the background paper uses 'CRISPR' and 'genome editing technology' interchangeably. Where the issues under discussion are specific to genome editing with CRISPR this will be signposted in the text.

2 Human Genome Editing: Somatic and Germline

Participants in the debate around genome editing in humans draw a line between germline modifications and somatic modifications. The most salient distinction here is whether the genetic changes associated with genome editing will be passed down through generations.

Human somatic genome editing refers to the use of genome editing in human somatic cells; namely, all body cells except reproductive cells (gametes) and cells that give rise to gametes. Somatic genome editing enables targeted editing in patients' cells of genes responsible for hereditary monogenic disorders, infectious diseases and cancer (16, 17). It is envisaged as a possible future treatment for patients affected by HIV (18); progressive blindness (19); haemophilia (20); cancer (21); sickle-cell anaemia (22); and cystic fibrosis (23) among other conditions. Clinical trials testing CRISPR in somatic cells are already under way (24-27).

Germline genome editing refers to the use of genome editing in human reproductive cells (i.e. gametes and cells that give rise to gametes) and early stage human embryos. Germline genome editing would potentially enable targeted editing of genes responsible for monogenic disorders, for polygenic disorders and to spread resistance to infectious diseases⁷ (28-31). It would work by targeting harmful mutations in gametes or in IVF embryos created using the gametes of couples with a known risk of transmitting such disorders to their offspring (19, 28, 29). This use of genome editing consists of germline modification, whereby the edited genetic material of embryos and gametes can be inherited by future generations.

2.1 Ethical Issues in Somatic Genome Editing

In drawing an ethical line between somatic genome editing and germline genome editing, Lanphier et al. (32) argue that germline genome editing raises severe concerns, but important steps in advancing human health could be made with somatic genome editing. These and other authors contend that concerns about germline genome editing should not forestall basic and clinical research with CRISPR in somatic cells, because this research could lead to treatments for patients suffering from a range of disabling and severe conditions (33-36). Beyond those advocating for somatic genome editing, ethical appraisals generally fall into one of two camps, respectively clustered around the continuity or novelty that CRISPR-based genome editing offers.

CRISPR on a Continuum

⁷ The latter two of these applications are considered significantly less likely due to the limited knowledge of polygenic disorders and of the genes involved in conferring resistance to infectious diseases.

The first camp places somatic genome editing with CRISPR in a continuum with existing gene therapies carried out with other genome editing technologies. It denies that somatic genome editing with CRISPR raises specific or novel challenges, especially when juxtaposed with germline genome editing. Scholars arguing along these lines note if safety and efficacy standards are met, then somatic genome editing can be considered unproblematic (37). This position concedes that the use of CRISPR in somatic cells raises relevant ethical issues pertaining to safety assessment; risks/benefits calculation; protection of vulnerable subjects; informed consent; patient monitoring; and equity of access, among others (38, 39). However, they emphasise that such issues are not novel, but rather akin to existing ethical issues, controversies and challenges already addressed within previous debates about clinical research ethics and research to develop human gene therapies (38, 39).

Such a view – that somatic genome editing with CRISPR does not raise novel ethical issues – underlies the position of the organising committee of the 2015 International Summit on Human Gene Editing and of the 2017 US National Academies of Science, Engineering and Medicine (NASEM) report. Both the International Summit statement (40) and the NASEM report (41) conclude that existing and evolving regulatory frameworks for research aimed at developing gene therapies would be sufficient to ‘appropriately’ and ‘rigorously’ evaluate potential harms and benefits of somatic genome editing (40). They also conclude that existing regulatory mechanisms have proven to be successful in preventing unauthorised uses of research aimed at developing gene therapies and that similar standards will be applied to somatic genome editing basic and clinical research with CRISPR (41).

CRISPR as Unprecedented

In contrast to the NASEM conclusions (41), the second set of assessments positions somatic genome editing using CRISPR as something unprecedented, questioning the sufficiency of existing ethical and regulatory frameworks to effectively govern this technology (35, 42, 43).

These authors draw attention to the lack of coordination across jurisdictions about the criteria to assess clinical utility, safety and efficacy (35). They also observe that the high variability of “biological manufacturing processes” as well as the “individual patient-focused nature” of many gene therapies raise the question of whether different patient-specific CRISPR therapies would require their own individual approvals (35). Authors discussing Phase 1 CRISPR genome editing cancer trials question the scientific validity of these trials due to the ‘translational distance’ between the available pre-clinical evidence and the proposed trials (43)

Others adopting similar positions argue that any new experimental intervention raises questions pertaining to harm/benefit calculation, safety, informed consent, protection of vulnerable populations, equity of access and so forth (42). They contend that while these assessments might fall within established clinical research ethics frameworks, additional questions remain. Such questions concern whether current clinical trials principles and protocols are adequate to assess and regulate somatic genome editing with CRISPR; whether there will be a need for particular protection of participants considering the novelty of the technology; and the role of commercial companies in developing and offering treatments based on this technology, among others (42). Scholars advancing this set of assessments agree that the novelty of the technology offers an opportunity to rethink

existing mechanism of engagement with relevant stakeholders; to foster conversations on acceptable thresholds for harms and benefits; to revise clinical trials pathways for the development of gene therapies; and to discuss what constitute harm or benefit and by whom such harm and benefit should be borne or reaped (34, 35, 42).

2.2 Ethical Issues in Germline Genome Editing

Germline modification represents the greatest area of ethical controversy surrounding genome editing (44) and most consider the direct intergenerational effects as the key factor distinguishing it from genome editing in somatic cells (45-48).

The ethical debate on CRISPR began in March 2015 with the publication, in *Nature*, of a paper proposing a voluntary moratorium on germline genome editing (32). A month later, another paper addressing this use of genome editing appeared in *Science* and called for a ‘prudent path forward’ for germline genome editing (49). The authors were participants in a January 2015 retreat (held in Napa, California) that aimed to start a discussion of the “scientific, medical, legal, and ethical implications” of genome editing (49). The *Nature* and the *Science* papers were both reacting to a rumoured (later published) article in *Protein & Cell* that reported a study by Chinese scientists who used CRISPR on non-viable human embryos (50). Scientists and ethicists were quick to react to news of the Chinese study and provided diverse assessments of its ethical implications, which are outlined in the following sections.

In November 2018 it was reported that CRISPR was used to alter the DNA of embryos subsequently transferred to a woman, leading to a successful pregnancy and birth⁸ (51). Chinese scientist He Jiankui edited the genome of twin embryos, intending to make them resistant to human immunodeficiency virus (HIV) by disabling the gene CCR5 (51). This experimental intervention has been widely condemned. Concerns have focused on the lack of safety assessments; the lack of a thorough ethical review process; the adequacy of the informed consent document signed by the prospective parents; and the exposure of the twins to the risk of genome editing without a proportionate harm/benefit ratio (52-56).

Many would regard the first reported study of germline genome editing, in *Protein & Cell*, as basic research: a way of using the technology to test its precision and efficiency. In contrast, the work of He would be an example of clinical research. However, the sharpness of the distinction between basic and clinical research has been questioned. The 2018 Nuffield Council report described it as a “distinction without a difference, one that depends not on the practice itself, but on circumstances” (3). This view highlights that very similar knowledge and technical requirements are needed to conduct ‘basic research’ and to achieve genetic modifications in vitro. Further challenging the sharpness of this distinction are claims related to the use of genome editing technologies to study the mechanisms of early human development in embryos. This use of genome editing is often justified on the grounds that it could improve clinical use of IVF and shed light on the causes of early miscarriages. Moreover, the relative accessibility and ease to use of genome editing might mean that users “who are not part of the elite scientific community and are not socialised or engaged in the

⁸ The experiment has not been published in any peer-review journal.

public discourse” (3) might further blur the line between basic and clinical research (13). Despite this view, assessments within the ethical debate on germline genome editing most frequently make separate assessments based on whether the technology is used for basic or clinical research. The arguments are reviewed below.

2.2.1 Basic Research with Genome Editing on the Germline

Three topics of discussion are visible within the debate focusing on foundational research questions: the value of increased knowledge; research involving human embryos; and questions about oocyte donation and incrementalism.

Increased Knowledge

Several reasons in favour of conducting basic research with genome editing on human embryos have been advanced. These reasons include: improving the efficacy and precision of genome editing technologies themselves (38, 57); better understanding the differences between human and non-human animal developmental biology (38, 57, 58); generating preliminary data to improve somatic genome editing (57); and improving the understanding of genetic diseases by creating models for in vitro drug testing (28, 59). In addition, basic research with genome editing could increase the understanding of the mechanisms of early human development⁹. Ultimately, the hope is that this would have therapeutic implications such as addressing causes of early miscarriages and improving clinical uses of IVF (38). Lastly, genome editing’s potential to reduce the occurrence of genetic diseases, thereby improving the health of many worldwide, is considered a compelling reason in favour of conducting basic research with this technology (60). For these reasons, some ethicists argue that continuing genome editing research in human embryos should be considered a ‘moral imperative’ (60).

Research Involving Human Embryos

Germline genome editing research with human embryos involves the destruction of the embryos employed in research. For some authors this is ethically objectionable (16, 38, 61) because it fails to respect the moral status of embryos (62, 63), an issue that has been discussed since the early days of the debate on embryo research (64). While research on human embryos remains a contentious matter, scholars often draw ethical distinctions based on the source of the embryos. For instance, research with human supernumerary embryos (i.e. embryos created during IVF to establish a pregnancy that will no longer be used for this purpose) is often considered more ethically acceptable than research with human embryos created specifically for research purposes. This distinction is reflected in the various legislative approaches to governing embryo research (38, 65). While some countries allow the creation of embryos for research purposes, others only allow research on supernumerary embryos (65). As de Wert et al. (38) note, addressing some research questions with

⁹ Studying the mechanisms of early human development and differentiation was also the rationale behind the licence granted in 2016 to Dr Kathy Niakan (Francis Crick Institute) by the Human and Fertilisation Embryology Authority (HFEA) to study early lineage segregations in humans.

genome editing is likely to require embryos at the single-cell stage, which will present a governance dilemma for some legislators: the embryos will need to be created specifically for this purpose (i.e. they will not be supernumerary embryos originally created to establish a pregnancy), but many jurisdictions forbid this.

In addition to potentially challenging existing regulatory and ethical frameworks on how to obtain embryos for research purposes, the use of genome editing for basic research raises questions regarding existing limits to conduct research on human embryos. Recent developments in embryology have demonstrated that embryos can be sustained in vitro for 12-13 days (66, 67), which is longer than it was hitherto technically possible. In reacting to these studies, some have called for revisiting and potentially extending the 14-day statutory limit to conduct research on human embryos (68-70) (for a discussion of these proposals, see for instance: Baylis (71); Cavaliere (64); Chan (72)). This is relevant for the debate on genome editing as the rationale underlining both research on human embryos beyond the 14th day and research on human embryos with genome editing technologies is to better understand embryonic developmental biology and what genes are involved in the mechanism of gastrulation, which takes place around the 16/17-day after fertilisation (58, 70). Indeed, scientists have explicitly referred to the importance of using CRISPR to conduct research on embryos beyond the 14th day for these reasons (58). An open question with respect to these recent developments in embryology is whether conducting research with genome editing technologies on human embryos should be discussed jointly with extending the statutory limit beyond the 14-day. In both cases the key question seems to be whether sometimes longstanding regulation representing settled societal norms should be altered to allow for new research questions to be pursued by scientists.

Additional Ethical Concerns

With respect to basic research on human embryos with genome editing technologies, additional discussed issues include: the need to protect the women who supply the oocytes for germline genome editing research from the risks of coercion and exploitation (38); and slippery slope concerns (38, 73, 74). Slippery slope concerns take three forms: first, that allowing basic research in human embryos with genome editing may lead to future clinical research regarded as ethically troubling. Second, that allowing basic and clinical research with genome editing on human somatic cells may pave the way to eventually allowing basic and clinical research on the germline. The third set of concerns points to the risk of moving from 'therapeutic' to 'enhancing' uses of genome editing. Slippery slope concerns are often discussed in ethical debates on technological developments and have been discussed also with respect to germline genome editing (38, 73-75).

2.2.2 Clinical Research with Genome Editing on the Germline

While at present there seems to be widespread agreement among ethicists, scientists and expert bodies that it would be too soon to use CRISPR on gametes and embryos to correct mutations responsible for monogenic disorders, these uses are both the most discussed and most divisive matter within the ethical debate on genome editing technologies. Two main, interlinked, areas of dispute

can be identified: firstly, whether there is a need for germline genome editing; and secondly, questions relating to the assessment, and management, of safety and uncertainty.

A Need for Germline Genome Editing

Authors disagree about whether there is a need for CRISPR germline genome editing considering the risks involved and the availability of other technologies. Those in favour of using CRISPR to edit harmful mutations in embryos and gametes responsible for monogenic disorders contend that germline genome editing would enable the prevention of genetic diseases (28). Hence, some argue that the medical need for germline genome editing is so compelling that proceeding with this use of genome editing is a moral imperative (28, 29) and that doing so would help to 'lighten the burden of human existence' (31).

Currently, couples at risk of transmitting monogenic disorders to their offspring could opt to use IVF in connection with pre-implantation genetic diagnosis (PGD) as a means of conception. PGD screens the embryos created using IVF for the harmful mutation, meaning that only embryos without the mutation will be transferred to utero. PGD thus enables these couples to have genetically related children with a risk of inheriting their harmful mutation that is low or inexistent. The existence of a well-established and safe alternative to genome editing for monogenic disorders has led several authors to question whether there is a need for germline genome editing (73, 76). Countering this position are those who do not consider PGD and germline genome sufficiently different interventions to be in favour of the former and object against the latter (59); those who stress that, following PGD, there may be no mutation-free embryos available to be transferred; and those who argue that germline genome editing could correct harmful mutations when selected embryos for implantation are healthy carriers, thereby avoiding the risk of passing the genetic disorders to future generations (28, 29).

Genetic Relatedness

Germline genome editing would represent an alternative means to have genetically related children for couples affected by disorders for which PGD is ineffective. There are cases in which no unaffected embryo can be created and transferred in utero to establish a pregnancy¹⁰. At present, these couples could resort to alternative ways to pursue parenthood in which the child would be genetically related to either one or neither of them. A significant question about the need for germline genome editing hence hinges on a normative consideration: whether the desire of these couples to have a genetically related child is compelling enough to justify the introduction of a new technology. This issue has recently been discussed with respect to other novel technologies (77-79) and it often emerges in normative debates on assisted conception.

¹⁰ Cases in which gene editing would be the only option to have a genetically related offspring include for instance: Y chromosome defects; dominant genetic disorders where one of the prospective parents is homozygous; recessive genetic disorders where both prospective parents are homozygous (3, 4). In other cases, embryos created with IVF are likely to be affected by the genetic conditions that is sought to avoid (3, 4). These cases include for instance: dominant genetic disorders where both prospective parents are heterozygous; recessive genetic disorders where one prospective parent is homozygous and the other heterozygous among others.

Authors advance contrasting assessments of this consideration: for instance, Gyngell et al. (29) estimate that, every year, there are several hundred cases worldwide where germline genome editing would be the only option to create unaffected embryos. In their view, this is a not negligible number that would supply strong reasons in favour of pursuing germline genome editing. Countering this position, Mertes & Pennings (80) argue that germline genome editing would benefit only a very limited number of couples and thus question whether there is a need for germline genome editing. Additionally, authors advance contrasting assessments pertaining to the allocation of scarce resources (76), the preferences and freedom of prospective parents (3, 38, 41, 59, 76, 81) and impersonal considerations on reducing the incidence of genetic disorders (29).

Safety and Uncertainty

Germane to questions of medical need are questions of assessing the safety of this technology and dealing with uncertainty, which represent the second main area of controversy within the ethical debate on clinical research involving human germline genome editing. At present, several major limitations of genome editing technologies are known, including: limited on-target editing efficiency; incomplete editing resulting in mosaicism; inaccurate both on-target and off-target editing (16).

Safety questions are particularly salient with germline editing due to the difficulties in assessing long-term and intergenerational effects of germline modifications (38, 82-84). Authors advance diverging assessments of two issues: the first is whether germline genome editing is something exceptional due to the long-term effects on future generations; and the second is whether pre-clinical studies on germline genome editing would generate sufficiently reassuring data to go forward with clinical research. Concerning the first issue, many have concluded that germline genome editing is indeed exceptional and must be treated with extreme caution (32, 45, 49), a position that is reflected in the several pieces of legislation worldwide prohibiting germline genome editing (85, 86). Others, however, contend that assisted reproductive technologies, natural reproduction and many other kinds of interventions affect future generations (29, 30). Hence, they conclude, germline genome editing should not single out as exceptionally worrisome for its intergenerational effects. Concerning whether assessments of safety will ever yield data that allow to move from pre-clinical to clinical studies, what divides authors is not whether the safety of germline editing can be assessed, but rather 'how safe is safe enough' (38) considering the potential benefits of this technology (30), their risks (45) and the availability of alternatives (76).

Beyond Safety Concerns

Several authors warn against flattening ethical debates on germline genome editing to questions of safety and efficacy (87) and argue that the relevant ethical questions that this technology raises are not exhausted by an assessment of these two features (88, 89). Indeed, other ethical issues have been debated. These issues pertain for instance to the violation of future children's capacity to live as autonomous agents by designing their genetic makeup (cf. Habermas (90)) and by making decisions on behalf of the next generations without their consent ((48); for a critical discussion and rejection of this claim, see Harris (31)). Another concern, expressed by the statement of the UNESCO panel of

experts deliberating on germline genome editing, is that germline genome editing threatens the ‘equal and inherent human dignity’ of all human beings ((91); for a discussion and rejection of this claim, see de Miguel Beriain (46)). Related to respecting dignity by not altering the human germline is the idea of protecting the human gene pool as a distinctively collective heritage (61, 92).

Additional concerns discussed within debates on the ethics of germline genome editing pertain to inequality and shifting social norms. The diffusion of germline genome editing could exacerbate social inequalities if it becomes only accessible to and employed by individuals or countries that can afford it. As a result, it could exacerbate social inequalities at the individual- or country-level (3, 37, 41). Some criticise this view and contend that germline genome editing could instead contribute to redressing natural inequalities brought about by the genetic lottery (29, 38) (cf. Buchanan et al. (93)).

The diffusion of germline genome editing could also affect social norms and change what is considered acceptable in reproductive settings. One worry in this respect is that the reproductive freedom of prospective parents might be undermined by social pressure and expectations to avoid the conception of embryos or fetuses that carry harmful genetic mutations (3, 38). And that couples undergoing IVF would be pressured into using or expected to use germline genome editing technologies on their embryos (3).

Another, related, worry is that the diffusion of germline editing would further undermine the rights of disabled people and contribute to exacerbating negative views of the people living with the conditions that germline editing would seek to ‘correct’ (3, 38, 41, 61). The 2018 Nuffield Council report states that to avoid undesirable outcomes associated with shifting norms, “it is necessary to refocus consideration from the desirability of individual choices to the kind of society that those choices might bring about” (3). To this end, the report promotes the adoption of the principle of ‘social justice and solidarity’, according to which germline genome editing “should be permitted only in circumstances in which it cannot reasonably be expected to produce or exacerbate social division or the unmitigated marginalisation or disadvantage of groups within society” (3, 47) (on solidarity in biomedicine, see also: Prainsack & Buyx (94)).

A final matter of ethical concern is whether germline genome editing should be employed for enhancement purposes. This matter has been discussed by several reports on the ethics of germline editing (3, 41); it has been addressed in efforts of public engagement on this use of genome editing (7); and within scholarly debates on the ethics of germline genome editing (29, 37, 38, 61, 75). While at present this possibility is beyond both technical capacity and scientific knowledge, two issues are matter of controversy. The first concerns the longstanding debate on the distinction between treatment and enhancement (90, 95, 96). The second concerns whether germline genome editing should be employed only to edit harmful mutations or for wider scopes to increase the welfare of future persons (29).

3 Governance of Genome Editing

In addition to the ethical issues and challenges outlined above, the debate on human genome editing has focused on ethical-political questions about socially-just mechanisms of governance for this technology. Expert bodies’ conclusions and recommendations have included discussions of how genome editing should be regulated and what values and principles should guide the process of

institutional design (for an overview of the regulatory landscape, see for instance Charo (97) and Isasi et al. (86)). Broadly, these expert bodies recommended that genome editing should be regulated in ways that serve public interests (3, 41); and should be based upon a ‘broad and inclusive social debate’ (3). Several scholarly publications speak of the need to foster democratic forms of engagement by involving members of the public in decision making and supporting dialogue between different kinds of experts (citizens included). A select group of authors have proposed specific ways to enact these democratic processes (45, 87, 89, 98, 99).

Among these proposals, some have stressed the need to create a consortium of organisations with a declared interest in genome editing. This consortium would serve as a two-way bridge to connect people to science/policy debates on the one hand, and scientists/policy-makers with the people on the other (98).

Another proposal builds on the final recommendation of the 2015 International Summit statement (40) and encourages the creation of public engagement mechanisms that aim to produce broad societal consensus about future, potentially acceptable uses of genome editing (45, 82). To this end, consensus building should be based on mechanisms of deliberation that do not seek to achieve unanimity; that do not a priori discard certain types of knowledge; that consider a full range of views and that do not privilege elites (45). The deliberation process leading to consensus should be modelled on principles such as ‘responsibility’, ‘self-discipline’, ‘respect’, ‘cooperation’ and ‘struggle’ and aimed at finding common grounds without excluding dissenting voices (45).

Emphasis has also been placed on projects that would enable forms of ‘cosmopolitan ethics’ (89, 100); multidisciplinary approaches of a global nature (87, 101); inclusive debates; a responsible and ethical use of genome editing (101), and the creation of a ‘global observatory’ to coordinate these efforts (87, 89). The idea behind such a ‘global forum’ is to help determine how to steer science towards the values and needs of society; to include representatives of from different cultures, political allegiances and ethical positions (87); to not shy away from complex questions pertaining to ‘human rights, dignity and human integrity’; and to move beyond risk-benefit assessments (89).

Taken together, these proposals have argued for the need to broaden the voices and framings within dialogues about human genome editing in two ways. First, by including voices that are normally silenced due to power relationships linked to geography, expertise and hierarchies. Second, by focusing on a broad range of fundamental questions that are not grounded in, and answered by, scientific assessments of safety and efficacy.

One area of controversy in this respect has been whether participants to these debates should fulfil any ‘epistemic’ (i.e. some background knowledge about the technology discussed) or ‘affective’ conditions (i.e. an expansion of one’s sympathies to favour mutual engagement with others) (102). More specifically, while some authors have argued for setting some kind of standard to access deliberative processes (45, 99), others have advocated for forms of engagement that focus on fundamental questions of values, which would not necessarily need any standard to be met (103, 104).

4 Conclusions: Areas of Controversy and Open Questions

The present background paper has provided an overview and an analysis of the ethical issues raised by basic and clinical research with genome editing in human somatic and germline cells. In this last

section, key areas of controversy and open questions that could serve as a starting point for the work of the WHO Expert Advisory Committee are outlined.

With respect to clinical trials involving somatic cell genome editing, the present analysis has found that the main area of controversy concerns whether existing clinical research ethics frameworks and oversight mechanisms are adequate to accommodate ethical and regulatory challenges raised by this use of CRISPR. A question that remains open is whether clinical trials pathways for the development of gene therapies should be revised.

With respect to basic research with genome editing on the germline, the main areas of controversy lie in the sharpness of the distinction between basic, pre-clinical and clinical research on the germline with CRISPR; and in the possibility of “sleepwalk[ing]” into a new order as a result of uncontrolled technological momentum that results in poorly constrained evolution and diffusion of new technologies” (3). Three key questions deserve ethical attention: firstly, whether the benefits of basic research outweigh the risks of moving from basic research to clinical research too swiftly. Secondly, whether such research is desirable or it violates fundamental values and interests. Thirdly, what effects of allowing basic research with genome editing on the germline will have on ongoing debates on the ethics of embryo research and of extending the 14-day limit to conduct such research.

Clinical research involving germline genome editing and its possible future once proven safe and effective are the most contentious and debated aspects of this technology. Main areas of controversy concern whether there is a need for germline genome editing considering the potential benefits (e.g. in terms of increased reproductive autonomy of prospective parents and the welfare of future persons) *vis-à-vis* the existence of alternatives and the relative risks of the new technology, both for individuals and society. Additional areas of controversy concern whether there could ever be an agreement on what counts as ‘safe enough’ to move from pre-clinical to clinical research; whether the rights of disabled people may be undermined; and whether human dignity would be significantly compromised by allowing germline genome editing. These areas of controversy have been addressed by references to the human rights framework, solidarity, notions of welfare and social justice. Open questions remain concerning not only whether and, if so, how clinical research involving human germline genome editing should be allowed, but especially concerning how to prevent increases in inequality, the discrimination of disabled people, the weakening of social justice and solidarity that may result from the diffusion of germline genome editing.

With respect to governance of genome editing, two sets of questions, one practical and the other conceptual, remain open. The first set of questions pertains to how to move from proposals such as those outlined in the previous section to implementing these proposals in practice. The second set of questions pertains instead to what, if any, epistemic and affective conditions should be fulfilled to participate in debates on the ethics and governance of genome editing.

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