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POLICY

One small edit for humans, one giant edit for humankind? Points and questions to consider for a responsible way forward for gene editing in humans

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Abstract

Gene editing, which allows for specific location(s) in the genome to be targeted and altered by deleting, adding or substituting nucleotides, is currently the subject of important academic and policy discussions. With the advent of efficient tools, such as CRISPR-Cas9, the plausibility of using gene editing safely in humans for either somatic or germ line gene editing is being considered seriously. Beyond safety issues, somatic gene editing in humans does raise ethical, legal and social issues (ELSI), however, it is suggested to be less challenging to existing ethical and legal frameworks; indeed somatic gene editing is already applied in (pre-) clinical trials. In contrast, the notion of altering the germ line or embryo such that alterations could be heritable in humans raises a large number of ELSI; it is currently debated whether it should even be allowed in the context of basic research. Even greater ELSI debates address the potential use of germ line or embryo gene editing for clinical purposes, which, at the moment is not being conducted and is prohibited in several jurisdictions. In the context of these ongoing debates surrounding gene editing, we present herein guidance to further discussion and investigation by highlighting three crucial areas that merit the most attention, time and resources at this stage in the responsible development and use of gene editing technologies: (1) conducting careful scientific research and disseminating results to build a solid evidence base; (2) conducting ethical, legal and social issues research; and (3) conducting meaningful stakeholder engagement, education and dialogue.

Introduction

Gene editing, which allows for specific location(s) in the genome to be targeted and changed by deleting, adding or substituting nucleotides, is currently the subject of much academic, industry and policy discussions. While not new per se, gene editing has become a particularly salient topic primarily due to a relatively novel tool called CRISPR-Cas9. This specific tool distinguishes itself from its counterparts, (e.g., zinc-finger nucleases and TAL effector nucleases (TALENs)) due to a mixture of increased efficiency (number of sites altered), specificity (at the exact location targeted), ease of use and accessibility for researchers (e.g., commercially available kits), as well as a

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relatively affordable price [1]. These attributes make CRISPR-Cas9 an extremely useful and powerful tool that can (and has) been used in research in order to alter the genes in cells from a large range of different organisms, including plants, non-human animals and microorganisms, as well as in human cells [2]. Ultimately, CRISPR-Cas9 is becoming increasingly available to a larger number of scientists, who have used it, or intend to use it for a myriad of reasons in many different research domains. When such powerful and potentially disruptive technologies or tools (begin to) show a tendency to become widely used, it is common for debate and discussion to erupt. Germane to this debate is the fact that with the advent of CRISPR-Cas9 and other similar tools (e.g., CRISPR Cpf1), the possibility of using the technique of gene editing in a potentially safe and effective manner in humans—whether for somatic or germ line/heritable[1] gene editing—has become feasible in the near to medium future.

With some clinical trials underway, somatic genetic editing for therapeutic purposes is certainly much closer to being offered in the clinic. For example, several clinical trials on HIV are ongoing [3, 4]; in 2015 an infant with leukaemia was treated with modified immunes cells (using TALENs) from a healthy donor [5]. Moreover, in the autumn of 2016, a Chinese group became 'the first to inject a person with cells that contain genes edited using the CRISPR-Cas9 technique' within the context of a clinical trial for aggressive lung cancer [6]. With such tools, gene editing is being touted as a feasible approach to treat or even cure certain single-gene diseases such as beta-thalassaemia and sickle-cell disease through somatic gene editing [3].

Beyond somatic cell gene editing, there is also discussion that through the manipulation of germ line cells or embryos, gene editing could be used to trans-generationally 'correct' or avoid single-gene disorders entirely. Notably, (ethical) concerns about heritable gene editing in humans were heightened when in April 2015, a group at Sun Yat-sen University in Guangzhou, China, led by Dr. Junjiu Huang reported they had successfully used gene editing in human embryos [7]. They used CRISPR-Cas9 to modify the beta-globin gene in non-viable (triplonuclear) spare embryos from in vitro fertility treatments. The authors concluded that while the experiments were successful overall, it is difficult to predict all the intended and unintended outcomes of gene editing in embryos (e.g., mosaicism, off-target events) and that 'clinical applications of the CRISPR-Cas9 system may be premature at this stage' [7]. Partly in anticipation/response to these experiments and to the increasing use of CRISPR-Cas9 in many different areas, a number of articles were published [2, 8–14] and meetings were organized [9, 10, 15–17] in order to further discuss the scientific, ethical, legal, policy and social issues of gene editing, particularly regarding heritable human gene editing and the responsible way forward.

Internationally, some first position papers on human gene editing were published in 2015 and 2016. Interestingly, these different recommendations and statements do not entirely concur with one another. The United Nations Educational, Scientific and Cultural Organisation (UNESCO) called for a temporary ban on any use of germ line gene editing [18]. The Society for Developmental Biology 'supports a voluntary moratorium by members of the scientific community on all manipulation of pre- implantation human embryos by genome editing′ [19]. The Washington Summit (2015) organizers (National Academy of Sciences, the U.S. National Academy of Medicine, the Chinese Academy of Sciences and the U.K.'s Royal Society) recommended against any use of it in the clinic at present [17] and specified that with increasing scientific knowledge and advances, this stance 'should be revisited on regular basis' [17]. Indeed, this was done, to some extent, in a follow-up report by the US National Academy of Sciences and National Academy of Medicine, in which the tone of the recommendations appear much more open towards allowing germ line modifications in the clinic [20, 21]. Meanwhile, the 'Hinxton group' also stated that gene editing 'is not sufficiently developed to consider human genome editing for clinical reproductive purposes at this time' [22] and they proposed a set of general recommendations to move the science of gene editing ahead in an established and accepted regulatory framework. Despite these differences, at least two arguments are consistent throughout these guidance documents: (1) the recognition of the need for further research regarding the risks and benefits; and (2) the recognition of the need for on-going discussion and/or education involving a wide range of stakeholders (including lay publics) regarding the potential clinical use and ethical and societal issues and impacts of heritable gene editing. It should be noted, however, that in the 2017 National Academies of Science, and of Medicine Report, the role of public engagement (PE) and dialogue was presented within the context of having to discuss the use of gene editing for enhancement vs. therapy (rather than somatic vs. heritable gene editing, which was the case in the 2015 summit report) [20, 21].

Although many stakeholders, including scientists, clinicians and patients are enthusiastic about the present and potential future applications of these more efficient tools in both the research and clinical contexts, there are also important concerns about moving forward with gene editing technologies for clinical use in humans, and to some extent, for use in the laboratory as well. As we have learned from other ethically sensitive areas in the field of genetics and

[1] In this category, we include the editing of germ line cells, or embryonic cells, or even somatic cells that are edited and promoted to then become germ line cells in such a way that the alterations would be heritable.

genomics, such as newborn screening, reproductive genetics or return of results, normative positions held by different stakeholders may be dissimilar and even completely incompatible. This might be influenced by various factors, such as commercial pressure, a technological imperative, ideological or political views, or personal values. Furthermore, it is clear that associated values often differ between different stakeholder groups, different cultures and countries (e.g., where some may be more/less liberal), making widespread or global agreement on such criteria very difficult, if not impossible to reach [23, 24].

From this perspective, it was important to study the opportunities and challenges created by the use of gene editing (with CRISPR-Cas9 and other similar tools) within the Public and Professional Policy Committee (PPPC)[2]of the European Society of Human Genetics (ESHG; https://www.eshg.org/pppc.0.html). Our committee advances that ESHG members and related stakeholders should be aware of, and if possible, take part in the current debates surrounding gene editing. Although not all genetics researchers will necessarily use gene editing in their research, and while gene editing as a potential treatment strategy, may appear, initially, somewhat separate from the diagnostics-focused present day Genetics Clinic, we believe that these stakeholders have an important role to play in the discussions around the development of these tools. For one, their expertise in the science of genetics and in dealing with patients with genetic diseases makes them a rare set of stakeholders who are particularly well placed to not only understand the molecular aspects and critically assess the scientific discourse, but also understand current clinic/hospital/health system resources, as well as human/patient needs. Furthermore, in more practical terms, one could consider that clinical genetics laboratories could be involved in the genome sequencing needed to verify for off-target events in somatic gene editing; and that clinical geneticists and/or genetic counsellors could be involved in some way in the offer of such treatment, especially in any counselling related to the genetic condition for which treatment is sought.

The PPPC is an interdisciplinary group of clinicians and researchers with backgrounds in different fields of expertise including Genetics, Health Law, Bioethics, Philosophy, Sociology, Health Policy, Psychology, as well as Health Economics. As a first step, a sub-committee was assigned the task to specifically study the subject of gene editing (including attending international meetings on the subject) and report back to the remaining members. Subsequently, all PPPC members contributed to a collective discussion during the January 2016 PPPC meeting in Zaandam, The Netherlands (15–16 January 2016). At this meeting, a decision was reached to develop an article outlining the main areas that need to be addressed in order to proceed responsibly with human gene editing, including a review of the critical issues for a multidisciplinary audience and the formulation of crucial questions that require answers as we move forward. A first draft of the article was developed by the sub-committee. This draft was further discussed during the 2016 ESHG annual meeting in Barcelona (21–24 May 2016). A second draft was developed and sent out for comments by all PPPC members and a final draft of the article was concluded based on these comments. Although the work herein acts as guidance for further discussion, reflection and research, the ESHG will be publishing separate recommendations on germ line gene editing (accepted during the 2017 annual meeting in Copenhagen, Denmark).

In the context of the ongoing discussion and debate surrounding gene editing, we present herein three crucial areas that merit the most attention at this stage in the responsible development and use of these gene editing technologies, particularly for uses that directly or indirectly affect humans:

1. Conducting careful scientific research to build an evidence base.
2. Conducting ethical, legal and social issues (ELSI) research.
3. Conducting meaningful stakeholder engagement, education, and dialogue (SEED).

Although the main focus of this discussion article is on the use of gene editing in humans (or in human cells) in research and in the clinic for both somatic and heritable gene editing, we also briefly mention the use of gene editing in non-humans as this will also affect humans indirectly.

Conduct ongoing responsible scientific research to build a solid evidence base

The benefits, as well as risks and negative impacts encountered when conducting gene editing in any research context should be adequately monitored and information about these should be made readily available. Particular attention should be paid to the dissemination of the information by reporting and/or publishing both the 'successful' and 'unsuccessful' experiments including the benefits and risks involved in experiments using gene editing in both human and non-human cells and organisms (Table 1).

An evidence base regarding actual (and potential) health risks and benefits relevant to the use of gene editing in the human context still needs to be built. Therefore, a discussion needs to be held regarding what type of monitoring,

[2] This group studies salient ethical, legal, social, policy and economic aspects relating to genetics and genomics.

Table 1 Example of questions that should be addressed regarding building a scientific evidence base for gene editing

	Example of questions
Conduct ongoing responsible scientific research to build a solid evidence base, especially regarding risk and benefits	Are the current expectations and practices of sharing the results of academic and commercial research, especially with respect to the risks and benefits, adequate for the current and future field of gene editing?
	Should there be a specific system established for the (systematic) monitoring of some types of basic and (pre-) clinical research?
	If so, which type of research would be required to adhere to this? All research, or only the research conducted in human cells?
	Who should/will take responsibility for this monitoring or reporting? And, where will the money to organize and sustain these efforts come from?
	How could or should an informative long-term medical surveillance of human patients be organized?
	Following treatment, would patients be obliged to commit to lifelong follow-up? How would this be done while still respecting individual autonomy?
	For each of the above questions, we can also ask, who should decide the answers to these questions? Based on what criteria?

reporting and potential proactive search for any physically based risks and benefits should be conducted by researchers using gene editing. Hereby, various questions emerge: are the current expectations and practices of sharing the results of academic and commercial research adequate for the current and future field of gene editing? Should there be a specific system established for the (systematic) monitoring of some types of basic and (pre-) clinical research? If so, which stakeholders/agencies should or could be responsible for this? How could or should an informative long-term medical surveillance of human patients be organized? Following treatment, would patients be obliged to commit to lifelong follow-up? And, if relevant, how could long-term consequences be monitored for future generations? For example, if heritable gene editing was allowed, from logistical and ELSI perspectives, there would be many challenges in attempting to ensure that the initial patients (in whom gene editing was conducted), as well as their offspring would report for some form of follow-up medical check-ups to assess the full impact of gene editing on future generations while still respecting these individuals' autonomy.

Although the availability of results and potential monitoring are especially important in a biomedical context for all experiments and assays conducted in human cells, and especially in any *ex vivo* or *in vivo* trials with humans, relevant and useful information (to the human context and/or affecting humans) can also be gleaned from the results of experiments with non-human animals and even plants. Furthermore, as clearly explained by Caplan et al. [2], gene editing in insects, plants and non-human animals are currently taking place and may have very concrete and important impacts on human health long before any gene editing experiments are used in any regular way in the health-care setting. As such, while keeping a focus on human use, there should also be monitoring of the results in non-human and non-model organism experiments and potential applications [2]. Effects might include change of the ecosystem, of microbial environment, (including the microbiome, of parasites and zoonosis, which can involve new combinations with some disappearing, and/or new unexpected ones appearing), change to vegetation, which has a reflection on our vegetal food and on animals' food and natural niche [25]. All this will have an impact on the environment, and consequently on organisms (including humans) who are exposed to this altered environment, hence the monitoring of risks and benefits is very important. Especially with gene editing of organisms for human consumption (in essence, genetically modified organisms), it will be important to note that the absence of obvious harms does not mean that there are no harms. Proper studies must be conducted and information regarding these should be made readily available.

Table 2 Example of questions needed to be addressed for the ethical, legal, and social issues research (ELSI) of gene editing

Area	Example of questions
ELSI of somatic cell gene editing	Does the current legal framework need amendments/additions to address somatic gene editing? If so, who will further shape the legal framework for somatic gene editing?
	Do present clinical trial principles and protocols suffice?
	How will trials in somatic gene editing be conducted and evaluated?
	Do we need particular protection or status for patients in such trials?
	What procedures will be instilled for patients receiving such treatments (e.g., consent, genetic counselling, follow-up monitoring)?
	To what extent will commercial companies be able to, or be allowed to offer, potentially upon consumer request, treatments based on techniques where so much uncertainty regarding harms remains?
	Which health-care professionals will be involved in the provision of somatic gene therapy and the care of patients who undergo such treatments?
	How will we ensure fair access to such technology?
	How will we ensure that the use is driven by need and not the technological imperative?
	Who will decide on roles and responsibilities in this novel context?
	Based on what criteria will the eligible diseases/populations to be treated be chosen?
	How can we ensure that research funds are allocated to ELSI research proportional (in some way) to the amount of research on gene editing.
ELSI of heritable gene editing	Should gene editing of human germ line cells, gametes and embryos be allowed in basic research—for the further understanding of human biology (e.g., human development) and without the intention of being used for creating modified human life?
	Should gene editing of germ line cells, gametes or embryos or any other cell that results in a heritable alteration be allowed in humans in a clinical setting?
	What, if any principles or reasoning would justify the use of hereditary gene editing in humans in a clinical context given the current ban on such techniques in many jurisdictions?
	Why should we consider using heritable gene editing in the clinic if there are alternative ways for couples to have healthy (biologically related) children? Who will decide? Based on what criteria?
	Should we first understand the risks and benefits of somatic gene editing before even seriously considering heritable gene editing?
	What are the roles, and responsibilities of different actors in these decisions?
	How do commercial incentives and the technological imperative play a role in these decisions?
	If we do entertain its use, what, if any criteria, will be safe enough according to different stakeholders (scientists, ethicists, clinicians, policy makers, patients, general public) for it to be legitimate to consider using gene editing for reproductive use? Who will set this safety threshold and based on what risk/benefit calculations?
	If heritable gene editing was allowed, how would the fact that for the first time, a human (scientist or clinician) would be directly editing the nuclear DNA of another human in a heritable way cause some form of segregation of types of humans? Creators and the created?
	If ever allowed, should heritable human gene editing be permitted only for specific medical purposes with a particular high chance of developing a disease (e.g., only when parents have a-near-100% risk of having a child affected with a serious disorder), and if so, would it matter if the risk is not 100%, but (much) lower?
	How can we, or should we define/demarcate medical reasons from enhancement? And, as was posed above for the use in somatic cells, for what medical conditions will gene editing be considered appropriate for use? What will the criteria be and who will decide?

Ongoing reflection, research and dialogue on the ELSI of gene editing as it pertains to humans

Research on the ELSI and impacts of human gene editing should be conducted in tandem with the basic scientific research, as well as with any implementations of gene editing in the clinic. Appropriate resources and priority should be granted to support and promote ELSI research; it should be performed unabated, in a meaningful way and by individuals from a diverse range of disciplines (Table 2).

Ongoing research, reflection and dialogue should address all ELSI[3] salient to gene editing. With respect to gene editing in humans, both somatic and germ line/heritable embryonic gene editing contexts should be addressed. As stated above, we should also study the ELSI of gene editing in non-human and non experimental/model organisms, including issues surrounding the potential (legal and logistical related to implementation) confusions surrounding the use of the terms genetically modified organisms vs. the term gene-edited organisms.

Somatic gene editing

Although somatic gene editing is not free from ethical, legal and social implications—it is, in many respects, similar to more traditional 'gene therapy' approaches in humans—it has been suggested that in many cases, the use of somatic gene editing does not challenge existing ethical, legal and social frameworks as much as heritable gene editing. However, as with any new experimental therapeutic, the unknowns still outweigh what is known and issues of risk assessment and safety, risk/benefit calculation, patient monitoring (potentially for long periods), reimbursement, equity in access to new therapies and the potential for the unjustified draining of resources from more pressing (albeit less novel) therapies, particular protection for vulnerable populations (e.g., fetuses, children (lacking competencies)), and informed consent remain important to study further [26].

Furthermore, as with any new (disruptive) technology or application, there often remains a gap to be filled between the setting of abstract principles or guidelines and how to apply these in practice. Indeed, important questions and uncertainties surrounding somatic gene editing both in research and in the clinic remain, including, but not limited to: do the established (national and international) legal and regulatory frameworks (e.g., Regulation (EC) no. 1394/2007 on advanced therapy medicinal products) need further shaping/revisions to appropriately address somatic gene editing (including not just issues with the products per se but also for issues related to potential health tourism)? And if so, how would this best be accomplished? Do present clinical trial principles and protocols suffice? How exactly will trials in somatic gene editing be conducted and evaluated? Do we need particular protection or status for patients in such trials? What procedures will be instilled for patients receiving such treatments (e.g., consent, genetic counselling, follow-up monitoring)? Furthermore, to what extent will commercial companies be able to, or be allowed to offer, potentially upon consumer request, treatments based on techniques where so much uncertainty regarding harms remains? Importantly, which health-care professionals will be involved in the provision of somatic gene therapy and the care of patients who undergo such treatments? Who will decide on roles and responsibilities in this novel context? And, based on what criteria will the eligible diseases/populations to be treated be chosen? Indeed, these questions can also all be applied to the context of heritable gene editing, which is discussed below.

Germ line/heritable gene editing

With respect to germ line or heritable gene editing in humans, the ELSI are more challenging than for somatic gene editing, yet they are not all new per se either. Some of these previously discussed concerns include, but are not limited to: issues addressing sanctity of human life, and respect for human dignity, the moral status of the human embryo, individual autonomy, respect and protection for vulnerable persons, respect for cultural and biological diversity and pluralism, disability rights, protection of future generations, equitable access to new technologies and health care, the potential reduction of human genetic variation, stakeholder roles and responsibilities in decision making, as well as how to conduct 'globally responsible' science [16, 2, 11, 18]. Discussions and debates over some of these topics have been held numerous times in the last three decades, especially within the context of in vitro fertilization, transgenic animals, cloning, pre-implantation genetic diagnosis (PGD), research with stem cells and induced pluripotent stem cells, as well as related to the large scope of discussion around 'enhancement' [13]. Although it is important to identify and reflect on more general ELSI linked with heritable gene editing and these different contexts, it is also vital to reflect on the ELSI that may be (more) specific to this novel approach. For example, would the fact that for the first time a human (scientist or clinician) would be directly editing the nuclear DNA of another human in a heritable way cause some form of segregation of types of humans? Creators and the created? [27] Clearly, we need time for additional reflection and discussion on such topics. Distinguishing the ELSI between different yet related contexts will allow for a deeper understanding of the

[3] Herein, the terms 'ethical', 'legal' and 'social' are used in a broad sense, where, for example, issues such as economic evaluations, public health prioritization and other related areas would also be included. Indeed the first goal of 'SEED' (see below) is also, to some extent, part of ELSI research, however, given the paucity of meaningful PE in the past, combined with strong consensus regarding the current need and importance of such activities, we have chosen to highlight it separately. We also wish to stress the difference between academic ELSI research and the work of ethics review committees. Although both deal with ethical and legal issues, the former has as a main goal to advance research and does not act as a policing body, nor does it have an agenda per se. Furthemore, ELSI research does not only identify issues to be addressed but also works with scientists and policy makers to address the issues responsibly.

issues and the rationale behind their (un)acceptability by different stakeholders.

A major contextual difference in the current discussions regarding germ line/heritable gene editing is that we have never been so close to having the technology to perform it in humans in a potentially safe and effective manner. Hence, as we move closer to this technical possibility and as we work out the scientific issues of efficiency and safety, the discussions orient themselves increasingly towards the ELSI regarding whether or not we want to even use heritable gene editing in a laboratory or clinical setting, and if so, how we want it to be used, by whom and based on which criteria? This includes, but is not limited to the following questions: should gene editing of human germ line cells, gametes and embryos be allowed in basic research—for the further understanding of human biology (e.g., human development) and without the intention of being used for creating modified human life? Some jurisdictions, such as the UK, have already answered this question, and are allowing this technique in the research setting in human cells in vitro (they will not be placed in a human body, the research will only involve studying the human embryos outside of the body) whereby researchers need to apply for permission to conduct such research. Some believe that allowing this will inevitably lead to the technology being used in the clinic (the so-called 'slippery slope' argument). This, then, brings us to the question at the centre of the debate: should gene editing of germ line cells, gametes or embryos or any other cell that results in a heritable alteration be allowed in humans in a clinical setting? Germane to this issue is another vital question: what, if any, principles or reasoning would justify the use of hereditary gene editing in humans in a clinical context given the current ban on such techniques in many jurisdictions? The new EU clinical trial Regulation (536/2014 Art 90 al.2.) does not allow germ line modification in humans. Should there be leeway for reconsidering this ban in the future in view of the possible benefits of therapeutic germ line gene editing? Should we first understand the risks and benefits of somatic gene editing before even seriously considering heritable gene editing? If we consider that it could be used in some situations, should we only consider using germ line gene editing in the clinic if there are absolutely no other alternatives? Should already established and potentially safer[4] reproductive alternatives, like PGD, be the approaches of choice before even considering germ line gene editing? If we do entertain its use, what, if any criteria, will be safe enough according to different stakeholders (scientists, ethicists, clinicians, policy makers, patients, general public) for it to be legitimate to consider using gene editing for reproductive use? Who will set this safety threshold and based on what risk/benefit calculations? Furthermore, if ever allowed, should heritable human gene editing be permitted only for specific medical purposes with a particular high chance of developing a disease (e.g., only when parents have a-near-100% risk of having a child affected with a serious disorder), and if so, would it matter if the risk is not 100%, but (much) lower? In addition, how can we, or should we define/demarcate medical reasons from enhancement? And, as was posed above for the use in somatic cells, for what medical conditions will gene editing be considered appropriate for use? What will the criteria be and who will decide?

Taking a step back and looking at the issues from a more general perspective, such ELSI research and reflection will need to address, among others, questions that fall under the following themes:

- the balance of risks and benefits for individual patients and also for the larger community and ecosystem as a whole;
- the ethical, governance and legislative frameworks;
- the motivations and interests 'pushing' gene editing to be used;
- the roles and responsibilities of different stakeholders in ensuring the ethically acceptable use of gene editing, including making sure that every stakeholder voice is heard;
- the commercial presence, influence, and impact on (the use of) gene editing;
- the rationale behind the allocation of resources for health care and research and if and which kind of shift might be expected with the new technologies on the rise.

Additional overarching issues relating to ELSI include the need to take a historical perspective and consider previous attempts to deal with genetic technologies and what or how we can learn from these; the need to consider how group actors could or should accept a shared global responsibility when it comes to the governance of gene editing; the potential eugenic tendencies related to new technologies used to eliminate disease phenotypes; the responsibility of current society for future generations; the way different stakeholders may perceive and desire to eliminate (genetic) risk and/or uncertainty by using new technologies such as gene editing; and the potential role(s) different stakeholders, including 'experts', may inadvertently play in propagating a false sense of control over human health.

Although the human context is where much of the attention currently resides, and is indeed, the focus of this article, as mentioned above, we also stress that many concerns and ELSI also stem from the use of gene editing in non-human organisms (plants, insects and microorganisms), the study of

[4] It is important to note that despite attempts at addressing these issues, even for technologies such as PGD [28].

Table 3 Examples of questions to be answered regarding stakeholder, engagement, education and dialogue (SEED) for gene editing

	Example of questions
Planting SEEDs for gene editing	What are the roles and responsibilities of different stakeholders in setting up and maintaining responsible engagement, education and dialogue?
	What will, and what should be the role of scientists and other academics in this type of popular media communications, and engagement activties?
	Since PE can have different purposes, before each activity, we must consider: what are our goals? And, what method of engagement will best meet these goals?
	How will the multitude of voices we want to involve in PE be 'weighted' against each other?
	What role will different stakeholders' inputs and 'preferences' play in the debate and in the decision-making process?
	How do we make sure that all voices are heard?
	How will these voices be weighed and considered, if at all, in policy making?
	How can we ensure that public education will not be reduced to a token work package in science grants and/or to campaigns that try to convince for or against gene editing?
	How can we make sure that such public education and engagement is accessible to all, including in countries that may currently not have the resources to take on such 'SEED' activities?

which, could inform the human context. More importantly, given that the use of gene editing in these organisms is currently taking place in laboratories and, if released, some of these gene-edited organisms could have a large impact on the environment and society [2], the ELSI of gene editing in non-human organisms should also be seriously addressed. In this respect, the current debates over definitions and whether plants and non-human animals in which gene editing is performed are considered (legally) genetically modified organisms (GMOs) are particularly important to consider; indeed, this legal stance may be a misleading way to describe the scientific differences in practice. Moreover, the manipulation of definitions may also be used to circumvent the negative press and opinions surrounding GMOs in Europe. Last, but not least, the use of gene editing for the creation of biologic weapons is a possibility that must be discussed and adequately managed [2].

In order to ensure that the appropriate ELSI research is conducted to answer these myriad questions, ELSI researchers must ensure adequate understanding of scientific facts and possibilities of gene editing, ensure appropriate use of robust methods [29] to answer specific ELSI questions, as well as learn from previous research on related themes such as (traditional) gene therapy, reproductive technologies, and GMOs. Furthermore, funding will have to be prioritized for ELSI research. National and European funding agencies should ensure that ELSI funding is given in certain proportion to how much gene editing research is being conducted in the laboratory and (pre) clinical domain. In practice, this will mean ensuring that there are adequate review panels for stand-alone ELSI grants, which do not usually fall within any one traditional academic field (e.g., philosophy, law or social sciences). The requirement of including ELSI work packages within science grants may also be useful if such work packages are conducted by ELSI experts (and this is verified by the funding agencies), that they are given enough budget to conduct research and not only offer services, and that the ELSI work package is not co-opted by the science agenda. Spending money on ELSI research has already allowed for the information to be used in more applied ways. Among others, ELSI research has contributed to helping individual researchers understand what kind of research they are (not) allowed to do in certain countries or regions; helped to design appropriate consent forms for research and clinic; and has helped inform policy decisions.

As ELSI are identified, studied and discussed, it will be of utmost importance to communicate these with as many publics as relevant and possible in a clear and comprehensive way so that the largest number of different stakeholders can understand and engage in a discussion about these issues. With respect to engaging non-academic and non-expert audiences in meaningful dialogue, the challenges are greater. Yet, as this is a vital element of conducting science and preparing clinical applications in a responsible manner and stretches beyond the academic focus of ELSI we propose to distinguish a third domain dedicated to such stakeholder engagement, education and dialogue (SEED) described below.

Stakeholder engagement, education and dialogue (SEED)

To deliver socially responsible research (and health care), an ongoing robust and meaningful multidisciplinary

dialogue among a diverse group of stakeholders, including lay publics, should be initiated and maintained to discuss scientific and ethically relevant issues related to gene editing. Publics must not only be asked to engage in the discussion, but they should also be given proper information and education regarding the known facts, as well as the uncertainties regarding the use of gene editing in research and in the clinic. In this way, the two focal areas described above will feed into these SEED goals. Stakeholders should also be given the tools to be able to reflect on the ethically relevant issues in order to help informed decision making. Appropriate resources and prioritization should be granted to support and promote SEED (Table 3).

As mentioned in the introduction, the statements addressing gene editing published by different groups and organizations have highlighted the need for an ongoing discussion about human gene editing among all stakeholders, including experts, and the general public(s) [8, 9, 17], In calling for an 'ongoing international forum to discuss the potential clinical uses of gene editing', the organizing committee of the International Summit on Human Gene Editing stated that

> 'The forum should be inclusive among nations and engage a wide range of perspectives and expertise – including from biomedical scientists, social scientists, ethicists, health care providers, patients and their families, people with disabilities, policymakers, regulators, research funders, faith leaders, public interest advocates, industry representatives, and members of the general public' [17].

Hence, this implies that not only should different expertise be represented in this ongoing discussion, but lay publics should also be included. For this to be a meaningful and impactful endeavour, all stakeholders involved should be appropriately informed and educated about the basic science and possibilities of gene editing. Academic/professional silos, differences in language, definitions, approaches and general lack of experience with multi- and interdisciplinary work are all barriers to involving different expert stakeholders in meaningful exchange and dialogue. Some first constructive steps have included the posting online of meeting and conference presentations on gene editing (e.g., the 3 days of the Washington Summit (http://www.nationalacademies.org/gene-editing/Gene-Edit-Summit/index.htm.), Eurordis webinars and meetings aimed at informing patients, http://www.eurordis.org/tv). Beyond this, one important barrier to having a truly meaningful and inclusive multidisciplinary discussion about new technologies is the (potential) lack of knowledge and/or understanding of different publics [30]. Indeed, it is not reasonable for experts to expect that all concerned stakeholders are properly informed about the science and/or the social and ethical issues, which are important requisites for having meaningful and productive conversations about responsible gene editing. Furthermore, a pitfall we must avoid is using PE with the aim of persuading or gaining acceptance of technologies instead of 'true participation' [31] and as a means to allow for supporting informed opinions.

Another critical issue is the role and influence of different stakeholders, including the media, in educating and informing the public. What are the roles and responsibilities of different stakeholders in setting up and maintaining responsible engagement and dialogue? What will, and what should be the role of scientists in popular media communications and other SEED activities? Where will the funding for these activities come from? Financial and temporal resources will have to be reserved for such SEED regarding gene editing. Resources will also be needed to conduct further research on the best way to engage different publics and to study whether engagement strategies are successful.

Moreover, before engaging different publics and asking for their feedback, whichever stakeholders take on this task must seriously reflect on the precise reasons for which lay publics are being engaged. What is the goal? And, what method of engagement will best meet these goals? There is also a need for honest evaluation of engagement efforts to report on their impacts and outcomes. Indeed, the purposes of PE in science can vary widely, including, among others, informing, consulting and/or collaborating; [32] clearly each of these implies different levels of participation by publics, and by extension, different levels of influence on a topic. Importantly, there are a long list of questions that also need to be answered for PE (Table 3), including but not limited to how different voices will be weighed and if or how they will be used in any policy or decision making.

The value of PE in the form of public dialogue in a democratic society, (and we would specify its contribution to responsible science) is very well summarized by Mohr and Raman (2012) in a perspective piece on the UK Stem Cell Dialogue: [31]

> 'The value of public dialogue in a democratic society is twofold. From a normative perspective, the process of PE is in itself a good thing in that the public should be consulted on decisions in which they have a stake. From a substantive standpoint, PE generates manifold perspectives, visions, and values that are relevant to the science and technologies in question, and could potentially lead to more socially robust outcomes (which may differ from the outcomes envisaged by sponsors or scientists)' [31].

Particularly for the purposes of gene editing, we consider SEED a way to try to ensure that decisions on a subject that is filled with uncertainties, and could have important

implications for society for generations to come, is not left in the hands of a few. We want to underline the need for: lay publics to be informed to support transparency; lay publics to be educated to support autonomy and informed opinion/decision making; different voices and concerns to be heard and considered through ongoing dialogue to help ensure that no one stakeholder group pursue their interests unchecked. Although it is beyond the scope of this article to go into any detail, it is important to take the time to learn from past and ongoing engagement efforts in science in general [32], as well as in biomedicine, including areas like stem cell research [31] and genetics [30, 33]. For example, we can learn about: how PE can generate value and impact for a society, as well as how to conceive of and evaluate a PE programme [32]; the nuances around 'representative samples' and if they really are representative [31]; how letting citizens be the 'architects' rather than just participants of engagement (activities) could help to ward against the generation of 'predetermined outcomes' [31]; the utility of deliberative PE to 'offer useful information to policy makers [30]. Given all the different reasons for PE, and given the higher standards expected for PE in recent years [34] it is to be expected that each PE activity will have to be adjusted for the specific context. There are, also, useful tools for PE from a European funded project called 'PE2020, Public Engagement Innovations for Horizon 2020' [35], which has as an aim to 'to identify, analyse and refine innovative public engagement (PE) tools and instruments for dynamic governance in the field of Science in Society (SiS)' [35].

As already mentioned above for ELSI research, funding agencies will have to prioritize resources for these SEED activities, and the strategies we outlined for ELSI, could also apply for SEED.

Conclusion

In the midst of a plethora of debate over gene editing, different stakeholder views, preferences, agendas and messages, it is crucial to focus our limited resources, including human resources, time and finances on the most important areas that will enable and support the responsible use of gene editing. We have identified the following three areas that merit an equitable distribution of attention and resources in the immediate and medium-term future:

1. Conducting careful scientific research to build an evidence base.
2. Conducting ELSI research.
3. Conducting meaningful stakeholder engagement, education, and dialogue (SEED).

Indeed, one way to ensure that each of these three important areas receive adequate financial support to conduct the necessary work would be for international and national funding agencies to announce specific funding calls on gene editing. They could also encourage or require that scientific projects focused on gene editing include ELSI and SEED along with the scientific work packages. Furthermore, understandably, priorities need to be made with respect to resource allocation in the biomedical sciences, especially in such uncertain financial contexts, however, as expressed at the World Science Forum in Budapest in November 2011, we must ward against scarce funding being funnelled to single disciplines since it is common knowledge that much of the most valuable work is now multidisciplinary [36]. Moreover, at such a time funding entities must not 'expel' the social sciences 'from the temple' but rather, the hard sciences should 'invite them in to help public engagement' [36].

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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