Perspective

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Personalized Medicine

The clinical application of gene editing: ethical and social issues

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Gene-editing techniques have progressed rapidly in the past 5 years. There are already ongoing human somatic gene-editing clinical trials for multiple diseases. And there has been one purported scenario of human germline gene editing in late 2018. In this paper, we will review the current state of the technology, discuss the ethical and social issues that surround the various forms of gene editing, as well as review emerging stakeholder data from professionals, the 'general public' and individuals and families dealing with genetic diseases potentially treatable by gene editing.

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For nearly 40 years, scientists and clinicians have aspired to treat genetic conditions in humans by altering genes or gene expression. While there were a number of attempts at early stage clinical trials [1], gene therapy approaches in the 1980's and 1990's were ultimately unsuccessful due to challenges in delivering functioning genes to the intended organ system and achieving sufficient gene expression for clinical impact. Only a few Phase III human clinical trials were initiated, with one ultimately ending in the death of a participant, Jesse Gelsinger, in 1999 [2]. In tandem to these developments, the international gene therapy policy framework has also evolved and streamlined, shifting the research context from an exceptional approach to the one governing general biomedical research [3–5]. In addition, across the world, somatic gene therapy in the clinical context continues to adopt a distinctive regulatory framework specially tailored for advance innovative therapies. This approach in many jurisdictions has created in turn an accelerated approval process and a new category for product classification such as the advanced therapy medicinal products or similar category adopted in Europe, the USA, Japan and Korea.

The past 5–7 years have brought significant progress in both gene therapy and 'gene-editing' tools, including zinc finger nucleases (ZFNs); transcription activator-like effector nucleases (TALENs) and clustered regularly interspaced short palindromic repeats (CRISPR) [6,7]. Such tools have become increasingly more efficient and technically easier to use [8], leading some to believe that they are ready for clinical translation in humans. By 2018,

several preliminary human somatic gene therapy trials, to treat hemoglobinopathies, hemophilia and lysosomal storage diseases such as MPS1, had been approved by regulatory agencies in the USA and Europe (e.g., LentiGlobin TDT for β-thalassemia, Luxturna for inherited retinal disease due to *RPE65* mutations) [9–12].

Germline gene-editing research in animals has already moved forward [13–15] and has transformed the way in which researchers make genetically modified animal models. While many countries have laws, professional guidelines or funding restrictions that limit or forbid human germline gene editing [16,17], a few have approved embryo research programs. For example, the Niakan laboratory in the UK was approved in early 2016 by the Human Fertilisation and Embryology Authority (HFEA) to do *in vitro* embryo research [18], and the Mitalipov laboratory in the USA published a paper describing *in vitro* human embryo editing in August 2017 [19]. Nevertheless, the world was shocked in November 2018 when He Jianku announced that he performed germline gene editing of the CCR5 gene in two recently born twins [20], particularly given that it appears the prospective parents may not have provided informed consent.

This paper will review the technical background of gene editing, as well as the ethical and policy issues that underlie it. We will describe research our teams and others are currently doing to address these ethical and policy issues, and propose key areas of research and policy work that are required before any further clinical translation of gene editing, particularly germline gene editing.

Technical background

Gene editing in humans can occur at various stages of the lifecourse: 'somatic' gene editing can occur during a pregnancy or after birth, while 'germline' gene editing takes place with germ cells (egg or sperm) or single-cell embryos (zygote). Somatic and germline gene editing differ with respect to the proportion of the body's cells that are edited. Somatic gene editing would typically affect a subset of cells, often confined to a single organ (e.g, blood, liver, muscle). Somatic gene editing could occur either in an *ex vivo* manner, with re-introduction into the body after treatment of targeted cells, or *in vivo*, where the editing tools are delivered directly into a patient's body. Germline gene editing would theoretically affect all of the cells in the person that arises from the edited germ cell or embryo, including that person's germ cells (except in cases of unintended mosaicism, where only a subset of the body's cells might be edited). Critically, germline edits would therefore be likely to propagate into future generations. Fetal somatic gene editing would represent a unique scenario in that it is intended to alter a subset of cells, like somatic gene editing, but because treatment occurs during fetal development, the hope would be that intervention can ameliorate or even prevent genetic conditions. However, fetal gene editing raises concerns regarding impacts on maternal health and the uncertainties of editing cells during crucial early development stages.

While all three types of gene editing have demonstrated feasibility in mammals [21–23], each has unique technical challenges in humans. Data on the potential risk of 'off-target mutations', mutations that occur at genomic sites other than the desired target site and therefore might introduce new disease risks (e.g., cancer), remain unclear. 'On-target mutations', or large insertions/deletions and complex rearrangements to the genomic site of interest, can also occur at the target site and potentially affect genes other than the target. It is also possible that even successful editing at the target site might confer undesirable consequences. For instance, the *CCR5* gene may confer resistance to the HIV virus but is thought to also confer greater susceptibility to West Nile virus and influenza [24,25]. There are complex considerations to be made in balancing the potential benefits against several possible harms.

Germline gene editing presents additional unique challenges. If gene editing succeeds in only editing some of the embryo's cells but not others, the embryo will be mosaic, which not only limits the potential therapeutic benefits but also potentially introduces unanticipated harms; using mosaic embryos of any kind in fertility procedures is highly controversial [26]. Many authors have pointed out the availability of other options for a healthy and biologically related child, including standard *in vitro* fertilization (IVF) coupled with preimplantation genetic testing that could identify embryos unaffected by the disease of concern [27]. There are only a few, very rare scenarios that would preclude any possibility of an unaffected and biologically related child using already available methods.

These scientific and technical challenges are likely to be surmountable given the rapid pace of progress in the gene editing field. Somatic gene editing in adults has already moved into clinical trials; in January 2018, the NIH launched the Somatic Cell Genome Editing research program to remove the barriers in implementing somatic gene editing into clinical care [28]. The Somatic Cell Genome Editing initiative includes improving current delivery mechanisms, gene editors and assays for testing the safety and efficacy of gene-editing tools. With this program, NIH hopes to accelerate the field and to expedite the translation of gene-editing treatments into meaningful clinical applications [29]. Sickle cell disease, in particular, has been recognized as a promising target for both gene therapy

Table 1. Ethical issues with gene editing.

General (across all types)	• Unknown risks of harm and unintended consequences of the technology • Challenge of defining acceptable uses and medical conditions (including nonmedical or enhancement uses, medical tourism and biohacking) • Human subjects protection regulation and oversight • Inclusion of stakeholders' views in policy making • Addressing justice, solidarity and equity of access to successful technologies
Germline	• The impact on future generations • Legal and funding bans or moratoria on germline gene editing in many jurisdictions • Issues in preclinical embryo research, including the large number of research embryos needed and protection for research donors • The need for international consensus on oversight of germline gene-editing clinical trials
Somatic: prenatal (*in utero*)	• The need for physical intervention and potential harm to the pregnancy and/or the mother • Concerns about research to validate interventions, particularly given that these are often historically vulnerable populations
Somatic: childhood or adulthood	• Historical research misconduct and issues in vulnerable populations with no other treatment options • Pediatric concerns around potential developmental impact

and gene editing [30,31]; in September 2018 the National Heart, Lung, and Blood Institute (NHLBI) of the NIH announced new initiative to help speed the development of genetic therapeutic cures for sickle cell disease (SCD).

Social & ethical implications

Beyond the scientific and technical challenges, there are complicated social, ethical and policy questions, which we summarize in Table 1. All of these issues vary by cultural, social and political contexts, including religious perspectives on gene modification, assisted reproductive technologies and abortion; legal policies regarding fetal and embryo research and abortion; social attitudes toward disability and social inclusion; economic contexts of healthcare provision and social welfare programs; the political and social status of pregnant women, children and people with disabilities; and issues around a child's autonomy and right to an open future. It also bears repeating that somatic gene editing differs from germline and fetal gene editing in the potential to affect other individuals besides the intended patient, whether currently living or in the future.

The critical value of stakeholder research & engagement

There are numerous policy and professional guidance statements that we are aware of around the appropriate use of gene-editing technologies in humans [32–39] and we have summarized some of the key concepts they express in Tables 2 & 3. These statements generally share a call for research on stakeholder views, especially patient and disability groups, prior to the clinical translation of gene editing in order to contribute to set research priorities and to inform the development of related policy and regulatory approaches. For example, the European Society of Human Genetics states: "particularly for the purposes of gene editing, we consider SEED (Stakeholder engagement, education and dialogue) 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" [40]. But what does this really mean? Who does it include? Why do it? And how do we ensure that the expectations, interests and priorities of a diverse public are implemented in policy setting, particularly around germline gene editing.

In formulating any health policy, engagement with end users such as patient/family stakeholder and broader citizenry is increasingly seen as critical, and is frequently required or legislated by many health policy bodies [41]. Formats for collecting such data can vary significantly, which may bias the data and make findings difficult to generalize. And the impact varies based on who is requesting the engagement – patient or public engagement inputs requested by a Ministry of Health, for example, are likely to have more of an impact on policies since they are commissioned by a decision maker than those initiated by researchers or foundations or other nondecision makers [42]. It is also worth noting that often what is labeled 'stakeholder engagement' is, in fact, efforts at 'public education' or top-down efforts to build support for an existing research plan or policy, rather than the kinds of collaborative and informed deliberation. For example, a recent review found that even the more robust attempts at stakeholder engagement commonly found in HIV research have tended toward 'researcher-driven, top-down methods', and toward early stage clinical trials rather than later stages with potentially more translational impact [43].

Table 2. Key terms in policy calls for 'public' engagement.

Dialog	Activities, strategies and methods should support dialog or engagement that is: • open or transparent • urgent and/or ongoing • responsible • participatory, inclusive or democratic • global (beyond local borders)
Objectives	Activities, strategies and methods should have as overarching goals to: • promote advocacy • stimulate communication, discussion or debate • educate or inform the target audience(s) • provide advice, serve as a mechanism for consultation and/or support decision-making processes • build (societal) consensus • empower stakeholder(s) engagement and influence in decision-making processes • facilitate issue identification (scientific, socio-ethical impact, etc.) and assessment (risks, scope, safety) • support governance mechanisms (e.g., ethics oversight) • inform policy-making efforts • review effects of extant policy or its absence (e.g., impact of bans, restrictions, moratoria) • build trustworthiness
Participants/target audience	Actors and target audience(s) in/for engagement efforts are: • stakeholders • 'lay', 'general' public or citizens • community (national and global) • society (e.g., local and international) • patients • research subjects/participants • caregivers and members of affected families • scientists and academics (individuals and professional organizations) • government (national, policymakers) and governance bodies (e.g., licensing authorities and ethics review committees) • funding agencies (private and governmental)

Table 3. Common themes in international and professional guidelines.

Scientific integrity and strength	Translation should be based only on robust, reproducible, scientific studies that demonstrate safety and efficacy
Clinical need	Gene-editing technologies should be used to target disease and improve human health. Conditions that have valid and effective medical interventions should not take priority
Precautionary approach	Translation should move in a measured, conservative manner that builds on previous successes
Justice	In both clinical targets and access to treatment, translation should work to address equity and reduce health disparities
Human subjects protection	Existing bioethical principles and frameworks should be observed at all times to protect the autonomy of patients, research participants and families
Public engagement	The direction and pace of translation should be the ongoing subject of widespread engagement with stakeholder groups and publics

Collaborative efforts are more laborious and time consuming but result in more fully incorporating stakeholder perspectives. Additional challenges include identifying appropriate stakeholder groups, the reality that stakeholder interests will never fully align, and developing decision-making processes that balance and synthesize these divergent – even conflicting – interests.

When thinking about which conditions warrant gene editing, issues of disability and identity are important to consider. Members of the disability community have raised concerns about technologies to prevent the birth of children with disabilities (such as prenatal testing and preimplantation genetic diagnosis) and even 'cures' or treatments for some disabilities (such as cochlear implants; e.g. [44–52]). They believe that these technologies express and perpetuate negative attitudes toward people with disabilities: rather than accepting people with difference, medicine focuses on making them 'more normal'. Indeed, particularly reproductive approaches have been criticized for trying to eliminate traits that are a source of positive value and identity for many and constitute a form of human diversity [53]. Studies show that members of the general public and healthcare professionals underestimate the quality of life of people with disabilities compared with how they and their families report it, underscoring the importance of involving stakeholders with disabilities in research and policymaking [54–60].

Finally, we argue that conducting stakeholder research improves the research process and the quality of published research by impacting legitimacy, transparency and the quality of the policy decision [41,61–65]. Specifically, it

promotes a sense of inclusion and trustworthiness among and between stakeholders, which can help address the historic problem of recruiting underserved or under-represented populations (both in terms of ethnicity, for example, in the US communities participating in sickle cell research, as well as communities of rare disease and individuals with disability potentially treated by gene editing). It can also impact approaches to consent, and improve clinical uptake because the relevant patient populations have been included in the development of new treatments from early in the process.

Voices of stakeholders

In response to the call for stakeholder data about attitudes toward gene editing, our various research groups have been involved in survey, interview and focus group data collection to document the attitudes of scientists, clinicians, the general public and patient/family stakeholder groups toward the various types of gene editing. Below, we will summarize the currently published data and some of our own work that is pending publication.

Attitudes of scientists & clinicians

The earliest studies of stakeholder views began by assessing the knowledge and attitudes of scientists and clinicians, due to their greater background knowledge of gene editing. Armsby *et al.* [66] presented work at the 2016 American Society of Human Genetics meeting on a survey that assessed attitudes of members of various genetics professional organizations across the globe. Five hundred respondents represented clinicians (56%), clinical lab (7%) and research scientists (30%), and Ethical, Legal, and Social Implications (ELSI) researchers and educators (5%) covering all continents. A second publication surveyed 300 scientists and physicians attending a cardiology professional society meeting in 2017 [67]. Both studies found high levels of support for somatic gene-editing research and clinical translation (as high as 70–85% depending on the specific scenarios), but lower support for germline gene-editing research and its clinical translation. In both studies, scientists and clinicians were significantly more supportive of therapeutic treatments (e.g., of physical or intellectual disability) in both somatic and germline settings than they were of enhancement treatments (e.g., improving appearance, physical abilities or cognitive abilities). Researchers also addressed whether concepts of severity influenced attitudes, although they examined it in slightly different ways. Armsby [66] found that penetrance, age of onset, impact of condition on lifespan and degree of impairment influenced hypothetical support, but overall prevalence of a condition did not. Musunuru *et al.* [67] found that the severity of the condition being treated by germline gene editing influenced the level of support, and that 61% found it acceptable to use germline gene editing to have a healthy biological child when there is no other means to do so (i.e., severe genetic disorder), but fewer (45%) found it acceptable to reduce the risk of having a serious medical condition during the lifetime.

Persaud *et al.* found that physicians who care for individuals with SCD [68], stressed the importance of discussing the range of therapeutic options available both within, and outside of the gene-editing research trials, as well as clearly explaining the purpose of Phase I clinical trials, and the implications and limitations, of participation.

> "*A patient needs to know that gene therapy may cure you only if you do it at birth. If you wait until you have already suffered a stroke, renal disease, whatever. . . even if you have gene therapy, this is not going to reverse the damage that has already occurred.*" (Physician [68]).

Last, participants urged researchers to act in a manner sensitive to the fraught past between the SCD patient community and researchers.

> "*I feel like we have one shot with this community. If things wane and we can't maintain whatever is the production of the cure, then will they have something else that they can move forward with?*" (Physician [68]).

'Public' attitudes toward gene editing

Recent studies have begun to address views toward somatic and germline gene editing by the general public and various citizen constituencies thereof. In 2016, the Pew Research Center surveyed approximately 2500 US adults; in 2017 [69], the National Academies of Science and National Academies of Medicine surveyed 1600 US adults [38]; and in 2018 yougov.com surveyed approximately 5000 UK adults [70]. Studies in China and Japan have also assessed public support for theoretical applications of gene-editing technologies [71,72]. In considering the results, however, it is critical to take into account that such studies may be biased by how the technology and its implications are described by the media and/or the survey tool itself and the prior knowledge (or lack thereof) that participants have. Prior studies in the USA have found limited understanding of genetic science and related concepts [73], although

CRISPR and related technologies are both too new to have been included in such studies and also have generated considerable media hype that has likely changed public understandings in unknown ways. To our knowledge none of the currently published studies of the general public have taken a deliberative approach where individuals were educated over a period of time and subsequently evaluated as to their attitudes. Each study also used slightly different wording, which can make comparisons challenging.

Despite these challenges, a key, and somewhat surprising, finding is that members of these general publics appear to have similar levels of acceptance toward both hypothetical somatic and germline gene editing: generally around 60–70% acceptance levels for therapeutically focused gene editing [38,69]. The major distinctions appear to lie in the intended uses of the gene editing (e.g., a therapeutic approach compared with nonmedical or enhancements). For example, the Pew study found that 72% supported germline gene editing for treatment of a serious disease a baby would have at birth; 60% for reduction of risk of a serious disease that could occur over the lifetime; and 19% for use in making a baby more intelligent [69]. The UK study found that 83% would support gene editing if 'you were carrying genes for a genetic disorder and ran the risk of passing them on to future children' but only 23% supporting using it to 'make your future children more intelligent' and 12% supported it to 'change your future children's appearance' [70].

Finally, in a qualitative study designed to elicit views on gene editing in human embryos and somatic gene therapy, focus group participants in the upper midwest of the USA showed results consistent with broader public assessments [74]. Focus group participants were generally supportive of the use of gene editing to prevent or treat serious or life-threatening congenital or adult-onset disease but were more ambivalent about using gene editing to treat multifactorial diseases that could potentially be treated through lifestyle changes. Most opposed using gene editing for nonmedical or enhancement purposes, such as selecting for superficial traits (eye or hair color) in offspring. Participants expressed hope that gene-editing interventions could be used to treat serious, progressive diseases that may potentially impact themselves or their families.

> "*Things that are life threatening diseases, I would attack those first. And things that are not so. . . It would be nice if my child had blue eyes, or something, I'd say, let's not mess with that.*"
> "*I can see this if it was able to work and they could figure out how to do it, it could be a huge thing for Alzheimer's. . . Also, Parkinson's.*" [74]

Participants also expressed concerns that this technology could have unforeseen consequences to human health or could be misused. Some participants feared vulnerable patients could be exploited by unethical scientists or physicians, stressing the need for oversight as this technology is implemented.

> "*I think with the testing (germline gene editing) there can be some side effects that might be undesirable and might be causing some other problems that might even be worse than what you're dealing with*" [74].

While it was evident that focus group participants had limited knowledge about genetics and/or the methodology of gene editing, the ethical concerns expressed by participants reflect the published literature cited above on attitudes in the general public, as well as the ongoing discussions by academic, industry and government stakeholders [74].

Common themes about gene editing across different disease group stakeholders

Within our various research teams, we have conducted surveys, interviews and focus groups that queried various patient and family stakeholder groups about their attitudes toward gene editing. Thus far, this has included parents of children with Down syndrome (DS [75]; qualitative work is ongoing, and includes comparisons to parents of children with more medically serious aneuploidies such as trisomy 13 and 18), adults with inherited eye disorders such as Leber congenital amaurosis (LCA) or retinitis pigmentosa [76], and adults and parents of children with SCD [68]. Our work has thus far focused on conditions where gene-editing trials seemed imminent and on areas of genetic disease that represent a range of features and, in some ways, identify stakeholder populations where a sense of community or identity has been documented in the literature.

Despite the differences in age of onset, clinical presentation and overall severity of physical and intellectual impairment involved with these conditions, we have identified a number of themes that appear to be crossing multiple populations: qualified optimism about the potential of gene editing; conceptual similarities and differences with previous interventions; a weighing of potential risks and benefits; the social implications of gene editing including impacts on self identity, acceptance and inclusion; and justice and access. Participants also express

unanswered questions they have about gene-editing technologies, including the unknown harms and concerns about the newness of treatments.

Qualified optimism about the potential of gene editing

Overall, a majority of participants across all our studies [68,75–77], demonstrated qualified optimism about the use of gene editing as a promising (and sometimes overdue) treatment, though it often came with expressions of worry or frustration. Individuals with inherited eye disease and parents of children with Down syndrome showed a mix of optimism and caution. For example, parents of people with DS were more divided over the acceptability of fetal gene editing to silence the extra chromosome 21, with half stating they would support such a therapy and a little less than half opposed to this intervention [75]. Some parents of people with DS expressed optimism that an intervention could improve their child's neurocognition or reduce the physical symptoms of DS. Parents who were hypothetically supportive of *in utero* chromosome silencing identified the potential increase in cognition as an important benefit, as they believed it would enable their child to more fully integrate into society and gain independence [77].

> "*I adore so many qualities about my daughter but if there was opportunity to improve cognition which would lead to more independence and confidence I would do it*": Parent of a child with DS [77].

However, parents of people with DS were divided on what they considered to be the most appropriate therapeutic target of a genetic intervention. Many parents expressed that they were more concerned with reducing the impact of physical health conditions associated with DS (such as, for example, congenital heart defects) than they were about improving their child's neurocognition [77]; these themes are borne out in our ongoing qualitative research [78].

> "*If I had to choose between typical IQ and typical physical condition. . . I would choose the healthy body*": Parent of a child with DS [77].

For people with inherited eye conditions, enthusiasm for the prospect of gene editing varied with attitudes toward their own visual condition, with some blind adults very enthusiastic due to their perception of blindness being highly negative in their lives, and others who were less troubled by their blindness feeling more neutral toward the idea of curing it. However, these latter individuals were often excited about the possibility of gene-editing treatment for other conditions that they felt were painful or life threatening [76].

The potential stage or timing of treatment was another area where we saw cautious optimism from multiple stakeholder populations [68,74,76]. For example, families of people with DS expressed that a somatic gene-editing intervention, even during a pregnancy may be too late to have a significant impact on the cognitive phenotype of Down syndrome [77]. For people with retinal dystrophies, participants voiced awareness that the timing of a somatic gene therapy intervention could make a big difference in effectiveness – both in terms of amount of vision restored and ability to adapt to vision – but some balanced this with concerns about the ability of minors to consent to such interventions, and of sighted adults to competently make these decisions for blind children [76].

> "*I think because parents know so little about blindness and generally have never met a blind person who was living successfully they're awash in ignorance and fear. And they're going to do what the doctors tell them, and doctors are no better informed than parents about reality of life as a blind person. So they're not going to get . . . what I might consider to be good information*" [76].

Conceptual differences & similarities with previous interventions

Some observers of the gene-editing debate have argued that assigning too much ethical weight to gene editing, as opposed to the other alternative treatments and lifestyle approaches that can be tried, amounts to a form of genomic exceptionalism. Especially in somatic applications, one could argue that there is little difference between a gene-editing application and a novel drug. Indeed, the US FDA regulates them in the same way. Even fetal applications may have material parallels in the expansion of prenatal surgeries to address structural abnormalities in the developing fetus. In both cases, there are strong models to suggest that the intervention can be effective, at least in some cases, but also significant known risks to both mother and fetus, often in the form of miscarriage or preterm birth. Even embryonic and germline interventions, though most commonly agreed upon in terms of ethical challenges, may have some parallels in the early days of *in vitro* fertilization and cryopreservation. Although not technically gene editing, modern-assisted reproductive procedures can involve considerable manipulation of gametes and embryos,

manipulations that, at least in the early days, might well have had considerable unintended consequences. In our research, both parents and affected individuals grapple with the fact that whether an intervention involves gene editing materially affects their willingness to accept it on behalf of themselves and their children. Prenatal and pediatric interventions also share complex moral questions about the role of parenting and what the duties of a future or current parent are to their offspring. One parent of a child with DS recalled, "*having a son who went through heart surgery, the doctor explained chasing perfection can do more damage than help. Basically leave well enough alone*."

Weighing of potential risks & benefits

All the participant groups we assessed stressed that no matter how great the potential benefits of any suggested intervention were, the risks may make it not worth it. Participants often focused in on potential treatment risks, including the concept of unintended negative effects and unknown impact [68,77].

> "*Injecting genes is in my opinion too far. Genetically modifying human beings, and without any knowledge of long-term effects? Nope*": Parent of a child with DS [77].
> "*I'm really talking about changing someone's DNA. There is always that unintended consequence. You do A, but with the unknown potential?*": Parent of a child with SCD [68].

Participants also stressed the remaining uncertainty about what the risks and benefits entail, and were able to articulate trade offs that they were and were not willing to make. Many parents indicated their support would depend upon the level of risk involved [68,77], particularly, if there were any chance it could potentially exacerbate disease severity [68,76]. Or would only partially impact their medical condition [76].

> "*The question I think for me would ultimately come down to a lot of details. One is the cost, another is the treatment procedures. The risk, the downside risks as well as the upside potential. And then whether it's something I'd have to do repeatedly, or is it like this one time thing . . . Because I do have some vision at this point in time, if there's a risk I could lose what I have, that would be a factor . . . And if we're talking about only a marginal increase in my vision . . . then I might be much less inclined than if we're talking about a large enough increase . . . that it would have a meaningful impact on the functional utility of the vision I have*": Patient with LCA [76].

The genetic nature of proposed interventions was, however, specifically mentioned in terms of its impact on reproductive choice and future offspring [68].

Social implications of gene editing: self identity, acceptance & inclusion

The expressivist arguments described above were articulated by participants across all our studies thus far. For example, many persons with visual impairments and parents of children with DS described a high quality of life and opposed the medicalization of their difference [76,79].

> "*Every single thing I was told has been wrong. My daughter is smart, is competent, independent*": Parent of child with DS [79].
> "*I personally wouldn't choose blindness as an early priority for this technology . . . I would be much more excited about something that could prevent or treat breast cancer, for example . . . .*": Patient with LCA [76].

A very interesting theme emerged in several interviews of individuals who themselves had a genetic condition, around identity as it relates to impairment and the potential impact of gene-editing technologies:

> "*I've already lived some of my life and I enjoyed it pretty damn good. And as I said, I love everything about it. And what if we gave that chance to an embryo and we didn't give them retinitis pigmentosa and maybe their life wasn't wonderful and great and we took away that retinitis pigmentosa . . . I'm not saying that it would have been, but . . . what I'm saying is that I don't think it's really truly up to us to decide that*": Participant with retinitis pigmentosa [76].

There were some respondents who worried treatments and technology created false hopes and delayed adjustment:

"*I really worry about this sort of chimera of hope that we're going to fix all these blind people and give them sight and it leads people to go through life waiting for cure rather than living a life. . . . and it just seems to be so stultifying, so ultimately emotionally damaging*": Patient with LCA [76].

Participants in several stakeholder groups [76] raised global issues around how gene-editing treatments could impact on evolution, both scientifically and socially, and the negative impact of losing heterogeneity in society, a sort of 'counter-eugenic logic' (Garland–Thomson, 2012). Parents of children with DS stressed the unique contributions of their child to society, including their role in teaching others tolerance and inclusivity, and others articulated that the burden should be on society to become more inclusive of those with intellectual or other disabilities, not to treat or cure the phenotypes [76,79].

"*We have been so blessed by him (son with DS) exactly the way he is. A world without Down syndrome seems sad too*": Parent of a child with DS [79].

"*I just don't want people to think, oh my goodness, don't worry blind people, so what if the unemployment rate amongst blind people is 70% . . . now with gene editing, all the blind people will be able to see and now they'll be able to be employed . . . society is going to think, oh no need to make accessibility our prime focus or making accommodations . . . because there will be no more blind people*": Participant with retinitis pigmentosa [76].

Interestingly, concerns about how the widespread adoption of gene editing may impact the disability community were a theme also spontaneously brought up by general public focus group participants. These participants stressed the societal benefits of diversity and the lessons that can be learned from the inclusion and acceptance of disabled people.

"*Maybe having people with disabilities teaches the rest of us more compassion or gives us more diversity in our community to give us a better perspective on what the variation in life is all about*": Public participant [74].

Finally, some participants, both members of the general public [74] and individuals with blindness [76] expressed fear that parents could be socially or financially pressured into accepting gene editing for their child's condition through the denial of social services or insurance coverage if genetic intervention is declined.

"*If you don't get your embryo fixed, you can't get paid for the expenses. I think it's a way off but it could happen*": Public participant [74].

Social implications of gene editing: justice & equity

The principle of 'fairness' is a core ethical and health equity principle to guide implementation of gene-editing research and clinical treatment. The National Academy of Science (NAS) report [38] describes fairness as the principle that 'requires like cases be treated alike, and that risks and benefits be equitably distributed (distributive justice). Responsibilities that flow from adherence to this principle include equitable distribution of the burdens and benefits of research; and broad and equitable access to the benefits of resulting clinical applications of human genome editing' [38].

Equity and fairness was a dominant theme expressed by patients and families of individuals with sickle cell [68] and inherited blindness [76]:

"*If this treatment becomes available to the public, will it be available to everyone equally? I am not rich, but I qualify. I have sickle cell. I struggle with it daily*": Patient with SCD [68].

"*The people who are left behind would be the people in the lower socioeconomic echelons. . . a lot of the impetus for developing technology that blind people can use and the impetus for fighting for laws and fighting for rights has come from people who have education, who have been raised to feel empowered and articulate. And who've had families who have been able to push for them. So if those people all disappear, who's going to fight for everybody else? They're going to be forgotten*": Participant with LCA [76].

The stakeholders in several studies questioned who will actually benefit from the gene editing. For example, the global burden of SCD is not in the USA and Europe, but primarily in sub-Saharan Africa and India. It is estimated that between 300,000 and 400,000 babies are born with SCD each year [80].

"*Because it's a minority illness, it doesn't get the consideration that it should*" [68].

Conclusion

Gene-editing technologies are rapidly moving toward clinical incorporation without clear knowledge of the potential benefits and harms. As the scientific research moves forward, parallel stakeholder research is critical in building trustworthy and transparent research agendas, and in developing national and international policies that reflect key priorities and concerns of stakeholders.

Future perspective

As novel gene-editing technologies move closer and closer to the clinic and the potential to treat genetic disease somatically and through germline editing approaches, many ethical, policy and translational challenges remain. As scientific and social science researchers, we must continue to identify relevant ethical questions from the perspective of a broad range of stakeholder groups, and to do so in parallel with clinical trials (moving beyond the thus far hypothetical assessments). We must also encourage ongoing engagement among biological scientists, patient advocates, and bioethics and humanities researchers with the skills and experience to conduct healthcare policy research. Several observers have called for novel approaches to building broader and more inclusive collaborations that take into account the complex ethical, social and legal implications of these burgeoning technologies [81].

At the same time, there are lessons to be learned from the clinical translation of science and technology in the past. There are some public health processes in place for translating genetic technologies (e.g., Evaluation of Genomic Applications in Practice and Prevention [EGAPP]). In particular, the precautionary role of patient and bioethics stakeholders may be compromised if they are viewed as being too embedded in the translational process, to the point where translational determinism – the idea that any form of successful translation is a necessary and *a priori* good – sets in, in which case they are often criticized for being co-opted. All stakeholders – researchers, clinicians, advocates, and health services and policy scholars – must remain aware that the prospect of saving lives and removing disease burden can override more precautionary approaches to scientific discovery and public health. The example of He Jiankui, who has claimed that his controversial application of embryonic gene editing was justified in the service of eliminating the HIV virus, is a stark example of how scientific ambition and a narrow focus on genetics as 'the answer' can lead to undesirable outcomes [82].

A typical normative approach is to call for public or stakeholder engagement so that policy decisions can reflect societal interests and values. These policies often emanate from national or international professional organizations or funding agencies and are seldom incorporated into laws or governmental regulations [35,83]. As such, these policies are usually nonbinding and legally unenforceable. In addition, they frequently fail to establish a concrete mechanism for implementation, or even to resolve differing views from different stakeholder populations. Yet the influence of such recommendations should not be underestimated. Acknowledging the role of public engagement in the deliberate policy-making process creates normative responsibilities for those in charge, making them accountable for potential inaction. Equally important is the role that funders and professional organizations play as agents for policy transfer: these institutions provide a mechanism for the development and dissemination of best practices and exert pressure on other stakeholders, including governments, to act accordingly.

One of the challenges in moving forward is arriving at an ethical policy decision. To do so, we must bridge the chasm between descriptive ethics (i.e., what people believe should be done) and normative ethics (i.e., what ethical principles oblige), perspectives that are sometimes considered irreconcilable [84]. However, using patient or public engagement methods in systematic and robust studies to elicit ethical values can be a first step toward such bridging. Empirical evidence from patient/public engagement can be used to excavate core values or principles, which can in turn be used to formulate concrete policies. Thus, patient/public engagement approaches to explore ethical issues can identify values and positions of communities, clarify meanings and perspectives of stakeholders, and ultimately portray the full complexity of the issues to enhance decision making and policy development.

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Executive summary

Background

- There are several currently used gene-editing techniques including clustered regularly interspaced short palindromic repeats, transcription activator-like effector nucleases and zinc finger nucleases.
- Somatic gene-editing clinical trials have already begun in humans for several diseases, with more set for 2019.
- Germline gene editing has been performed in animals, and there are publications on human *in vitro* studies. Human germline gene editing was reported in November 2018, but has not yet been published in a peer reviewed setting.

Technical background

- Safety and effectiveness data are still limited for all types of gene editing in humans.

Stakeholder research

- Research has addressed hypothetical attitudes toward somatic and germline gene editing in various professional groups, general publics (typically without deliberative education), and family and individuals faced with specific genetic diseases.

Common themes

- Common themes that arise in the available patient/family stakeholder research include: qualified optimism about the potential of gene editing; conceptual similarities and differences with previous interventions; a weighing of potential risks and benefits; the social implications of gene editing including impacts on self identity, acceptance and inclusion; and justice and access.

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