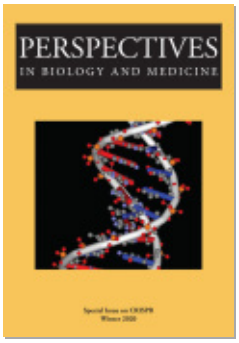
Focusing on Human Rights: a framework for CRISPR germline genome editing ethics and regulation



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Focusing on Human Rights

a framework for CRISPR germline genome editing ethics and regulation

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ABSTRACT The late 2018 announcement of the claimed births of CRISPR-edited babies has stimulated widespread condemnation and calls by some leading scientists for a moratorium on any further germline genome editing (GGE) for reproductive purposes. Concurrently, national and international bodies are calling for the development of robust guidelines and regulations that will identify permissible conditions under which such GGE efforts might eventually proceed. Crucially, these conditions go beyond rigorous safety standards to address some of the social and ethical concerns that arise with germline interventions. As these bodies convene to navigate this unique terrain, we suggest an important standard for generating ethically robust guidelines. Our approach builds from concerns about social exclusion and social justice with a focus on fundamental human rights. We believe that a deontological or rights-based approach, rather than a utilitarian approach, is needed to ensure that this socially disruptive technology minimizes further marginalization of people with disabilities and does not create a new form of social injustice. In pursuit of a deontological framework, we propose the implementation of an objective assessment tool: the Human Rights Impact Assessment (HRIA). Use of the HRIA establishes necessary constraints on applications of GGE in order to safeguard the most vulnerable members of society.

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THE RECENT ANNOUNCEMENT OF THE CLAIMED BIRTHS of CRISPR-edited babies has prompted both widespread condemnation and calls by leading scientists for a moratorium on any further germline genome editing (GGE) for reproductive purposes (Lander et al. 2019; Regalado 2018). Concurrently, national and international bodies are calling for the development of robust guidelines and requirements that will identify permissible conditions under which such GGE efforts may proceed (NAS 2017; Nuffield Council on Bioethics 2018a). As detailed recommendations to navigate this unique terrain are under development, we suggest an approach that begins with identifying serious concerns about social exclusion and social justice that arise with GGE. These concerns, we argue, are not captured by a utilitarian ethics framework, which seeks to maximize positive over negative health outcomes. Rather, these concerns reflect people's rights, rights that have standing independently of outcome assessment and that set constraints on the means to achieving an otherwise positive end like the goal of improving population health. To operationalize an approach that takes the promise of technologies to improve health seriously, while also constraining the means to this end according to rights considerations, we propose using the Human Rights Impact Assessment (HRIA) (Gostin and Mann 1994).

Before developing an effective regulatory framework with an emphasis on human rights, we must identify the distinct features that trigger societal concerns over GGE. The rapid and widespread emergence of discussions surrounding the CRISPR babies case confirms that scientists engineering heritable changes to human beings touches on something core to the human experience. This kind of genome editing goes beyond the conventional concerns about the safety and effectiveness of the technology. In contrast to GGE, applications of non-heritable genome editing tend to generate a more subdued response from both the public and the scientific or medical communities. For example, when undertaken in FDA-approved clinical trials, editing the CCR5 gene in adults with the goal of treating HIV infection was heralded as an important medical step forward (US National Library of Medicine 2018). Scientists involved in the CRISPR babies experiment targeted the same CCR5 gene, aiming to prevent HIV infection, yet many saw this milestone as a step backwards. This is not to say that all theoretical non-heritable genome editing applications are immune from societal concern. For example, genome editing for the purpose of restoring hearing in deaf communities can be seen as a cultural threat and a disruptive reframing of deafness as a detriment rather than a benefit (Scully 2008). Yet beyond these cases of polarizing non-heritable genome editing applications, GGE appears to encounter a volatile terrain of universal scrutiny and intense objection. In order to establish meaningful regulations, we must first understand the rationale underpinning these objections.

The Phantom Line Between Treatment and Enhancement

One theme running through the existing GGE regulatory recommendations, including the 2017 National Academy of Science (NAS) report on genome editing and the recent call for a moratorium on GGE published in *Nature* (Lander et al. 2019), suggests that treatment versus enhancement is a core societal concern. Polls have indicated a public uneasiness in using GGE to enhance a beneficiary rather than to address a severe unmet medical need, a distinction that the NAS and the moratorium authors use as a permissibility pillar (Pew Research Center 2018). However, a robust regulatory framework cannot stand upon such a distinction. The line between a treatment and an enhancement is blurry at best. First of all, the concepts of "treatment" and "enhancement" are context dependent. A treatment in one cultural or geographic setting, or at one period in history, may be an enhancement in another. For example, society's use of anti-cholesterol medications to prevent heart disease has increased as tolerable ratios of low-density lipoproteins to high-density lipoproteins has decreased, highlighting how society's health norms and standard of care evolve as new technologies are introduced. Since treatments may be defined as alterations that "restore [a person] to a normal state of human health and fitness" (President's Council on Bioethics 2003) and enhancements go beyond what is "normal," a constantly changing public health landscape can shift what was once an enhancement into the realm of normal medical care. Would germline editing of the PCSK9 gene to permanently reduce cardiac risk show a similar trajectory from enhancement to treatment if such a procedure became the standard of care?

Second, multiple reports have categorized the use of GGE to prevent disease as a therapeutic application, while such preventive measures may lead to human enhancement in multiple ways. Juengst and colleagues (2018) provide the example of altering the genome to increase expression of the Klotho protein to prevent degenerative neurological conditions. Increased production of Klotho has also been shown to enhance cognition in mice, an example of an "incidental enhancement." A fluctuating and non-discreet line between treatment and enhancement does not only occur under preventive measures to minimize risk, but also appears within the realm of targeted treatments, especially as the concept of a disease changes. For example, the idea of classifying aging as a disease is gaining support (Adam 2019). Slowing the process of aging would currently be considered an enhancement, but targeted genome editing of telomerase reverse transcriptase genes to minimize aging may be considered a germline treatment for a disease in the future (Tomás-Loba 2008). There are reasons such preventive or even targeted therapeutic germline edits are ethically problematic, which we turn to next, but those reasons cannot be pinpointed by drawing an enduring distinction between enhancement and treatment.

Social Justice and the Spectre of Eugenics

We need a much more robust account of what makes potentially valuable preventive alterations, such as editing the PCSK9 or CCR5 genes, ethically unacceptable at the embryonic stage. We see that account as based on two concerns, one about social inclusion and the spectre of eugenics, and the other about social justice. Note that both of these concerns were raised in an influential set of guidelines proposed by another national academic body, the Nuffield Council. The Nuffield Council on Bioethics report on genome editing and human reproduction stressed that GGE may be ethical if an alteration upholds "principles of social justice and solidarity, i.e. it should not be expected to increase disadvantage, discrimination, or division in society" (Nuffield Council 2018b, 1). Crucially, these are rights-based concerns. They depend upon the fundamental right of each person to be treated with equal regard and respect, which includes that each person has a fair chance at receiving a necessary and serious health benefit and that each person has a right to be protected from discrimination and social exclusion. We agree with the Nuffield Council that these rights-based concerns are central, necessitating a rights-based or deontological framework for GGE permissibility. In arguing for such a framework, let us specify how GGE poses threats to the concerns of social exclusion and social justice.

The issue of social exclusion arises when we consider how GGE may lead to the increased stigmatization of people with disabilities and even a potential slide into eugenics. GGE involves selecting out certain traits with the assumption that these traits make lives lesser lives. While this may seem like an understandably motivated selection against degenerative diseases like Huntington's disease, it could readily slide into selection against people with chronic disabilities who view their own lives as quite worth living but whom society devalues.

The paradigm case that has been raised is that of deafness. Although the medical community has viewed deafness as a disability worth preventing through cochlear implants, some deaf activists have seen this as an unwarranted intrusion that threatens the existence of their valued culture (including sign language and tightly knit social communities) (Weisberg et al. 2000). However, many other deaf people and families do not protest cochlear implants and appreciate this intervention. Perhaps the possibility of a somatic, post-birth genome edit, which individual families could independently decide on, would be greeted with similar mixed responses. However, a germline genome editing intervention is likely to create a different level of pressure to eliminate all deafness, a situation that resonates with the history of eugenics. Within an environment that allows the use of GGE for deafness, children born deaf could be even more isolated and stigmatized, and deaf culture extinguished. As an extension of this example, many other health differences could eventually become selected against through GGE, ranging from eyesight to cognition, leading to new targets of eugenics.

The fact that GGE raises the spectre of eugenics might be considered a full stop on considering GGE, but that is not the initial instinct of society. First of all, selection based on genetic traits is already accepted in the practice of pre-implantation genetic diagnosis (PGD), which some ethicists would argue is more offensive, insofar as it actually selects among potential lives (rather than among traits) to allow only embryos without the specified trait to develop. Despite this embryonic selection process, public protests about PGD are relatively infrequent, perhaps in part because PGD is not likely to scale to the level of overwhelming societal effects any time soon (*Gènéthique* 2015). PGD requires in vitro fertilization (IVF), a procedure with relatively low "success" rates, high price tags, and limited accessibility to much of society. Notably, though, GGE also requires IVF. Given that in 2012, only 1.5% of US births were conceived via IVF, it is unlikely that IVF rates will rapidly expand and incorporate GGE to a point of having a substantial species-level impact (CDC 2014). On the other hand, the costs for innovative technologies often decrease, while accessibility and success rates may improve over time. In either case, as those with the resources to access the technology increasingly use GGE to select against disabilities, any such use is likely to further exacerbate the social stigmatization and exclusion that marginalized communities experience. And on a practical note, societal commitments to assist people with disabilities are likely to diminish in a context in which more advantaged people can opt out.

This consolidation and inequality of implementation leads to the second major concern raised by GGE, one of broader social justice, which we would formulate as unfair aggregation of benefits. The technical requirements of GGE, along with the necessity of using IVF for implementation, assure that for the foreseeable future, access to the technology will be very costly. GGE would likely be another privilege of the wealthy, providing more health and other advantages that will not be fairly distributed.

There are important ethical arguments against aggregating too many forms of advantage in some persons over others, which we believe apply even more strongly to aggregating advantage in families across generations. Michael Walzer argued in *Spheres of Justice* (1983) that while a capitalist society could tolerate groups having dominance in some aspects of life—some in wealth, some in health, and some in education or civic leadership—it was patently unjust for some groups to have dominance across spheres. We know from research on the structural determinants of health that there is already entirely too much control over multiple spheres: economic disadvantage confers educational and health disadvantage. Surely, economically driven access to GGE would compound this aggregation of benefits significantly.

Thus we come to an important recognition regarding the ethics of GGE. In our view, the more serious ethical concerns regarding this technology arise because of existing intergenerational injustice in the distribution of health and other

benefits in our society, and because GGE, like many other expensive, innovative technologies, is poised to amplify such injustice. Nobel Prize winner Amartya Sen (1979) and Jerry Cohen (1989), perhaps the greatest thinker extending Sen's work, who has addressed the question of what comprises the basis of fairness in a free and just capitalist society, have both argued that fairness depends on equality of access to the advantages needed to pursue a good life. One need not reject market economies to see such heritable advantage as unfair—in fact, capitalism as we know it arose as an alternative to the dynastic, heritable control of wealth. Rejecting a heritable familial aggregation of benefits is as central to American values as it is to the values of people in the UK, expressed in their Nuffield guidelines.

A Human Rights Foundation for Ethical Frameworks

How do we move forward? Notably, a consistent thread appears in the various scientists calling for moratoria, self-policing, or other delays in GGE, as well as in both the NAS and the Nuffield reports. These statements all call for robust public debate that includes a broad spectrum of voices. This proposed exercise in popular governance of technological innovation has merit, due to its goal of including the many persons impacted in the decision-making process. However, simply creating the opportunity to participate in a debate does not ensure application of principles of social justice and inclusion/solidarity. Rather, there is a risk of simply replicating implicit biases, with majority or more empowered groups dominating others, as happened with rationing care in Oregon, where able-bodied people inadvertently ranked disability-related outcomes so low that disabled people were excluded from treatments (Bickenbach 2016). To prevent such dominance, it is essential to have transparent frameworks for ethical deliberation and decision-making—that is, explicit criteria and assessment tools. Further, given the challenge of including all possible and emerging voices on equal ground, absent such tools there is a risk of unbounded debate resulting in an indefinite outcome.

Despite these caveats, public engagement is imperative, and several groups, like the UK's National Co-ordinating Center for Public Engagement (NCCPE) and the Royal Society, have already begun approaching defined stakeholders and broad audiences (NCCPE 2018; van Mill, Hopkins, and Kinsella 2017). Beyond acquisition of input, translation into just and actionable policy requires robust and transparent ethical frameworks to contain societal debate and public, accountable, and logical arguments for applying such frameworks consistently and fairly. Thus, we would disagree with the *Nature* (NAS 2017) commentary: the commentary places hope in a five-year waiting time and public accountability, but it avoids suggesting any standards for what would count as ethical progress. The commentary states that: "The governance model we present would intentionally leave

room for nations to take differing approaches and reach different conclusions, informed by their history, culture, values and political systems. Still, the common principle would be all nations agreeing to proceed deliberately and with due respect to the opinions of humankind" (168).

We place less faith in the opinions of humankind and the politically expedient values of particular countries at particular times and more faith in international standards for human rights as a guide for approaching how to use CRISPR for GGE applications. There is abundant research in psychology, political science, and behavioral economics showing how public opinion can be highly unstable and is easily manipulated (Zaval and Cornwell 2016). But human rights stand above the political fray and set standards that protect every member of society. For example, we agree with Zeid Ra'ad Al Hussein (2019), former UN High Commissioner of Human Rights, that the ethical implementation of border-crossing technologies (artificial intelligence in his editorial) should not be ruled by local cultures or prevailing attitudes, but guided by a commitment to improving universal human rights. To this end, one framework for assessing the ethics of using CRISPR is to adapt the Human Rights Impact Assessment (HRIA) for addressing specific societal scenarios regarding GGE (Gostin and Mann 1994). The HRIA provides a public health approach for assessing whether the benefits of a given GGE application, given the societal context, outweighs disproportionate rights burdens and safeguards those vulnerable to rights infringements. This assessment is a compilation of seven questions, the specific details of which are beyond the scope of this article but discussed elsewhere (see Halpern et al. 2019). The assessment incorporates considerations of intrusiveness, efficacy, and targeting appropriate populations to avoid exploitation or exclusion. Practitioners of the HRIA have demonstrated its feasibility in areas that share ethical and public health features with the challenges of GGE, specifically the health rights of women (Bakker 2009).

There are some notable implications of choosing the HRIA as a core framework. Most important, it embodies a deontological, or rights-based approach to ethics, which is distinct from and can conflict with a utilitarian approach. To be specific, even if GGE would maximize some collective health outcome at a population level, either through preventive genome editing or targeted therapeutic approaches, if it violated the rights of distinct groups of people, such as people with disabilities, or if it created an irremediable unfair burden on the economically least well off, GGE would be unlikely to meet a robust standard of ethical appropriateness. A focus on human rights also aligns with the concerns of the Nuffield Council and helps establish constraints on applications of GGE across diverse cultures and societal norms.

A key aspect of utilizing an HRIA to evaluate the permissibility of GGE is the case-by-case nature of the approach. Under a utilitarian approach, insofar as GGE's permissibility depends on aggregate benefit over risk, incurable conditions

like Tay-Sachs may be edited regardless of unfair access based on the cost of such a procedure or the risk that wealthy people might then seek other germline genome edits. In contrast, implementation of an HRIA would take into account other available options, like improving access to genetic screening for Tay-Sachs, that might meet the needs of all and avoid opening the door to germline genome editing. Beyond health and wellness, the HRIA takes into account factors impacting population-level justice and equality, factors that are usually outside the scope of utilitarian approaches.

We understand that the *Nature* authors were rightfully observant of the problem that any substantive ethical framework, including an HRIA, may not be accepted by some countries. Our response to this is that such explicit frameworks are essential to make genuine ethical progress. We urge new bodies, such as the Global Observatory and the Association for Responsible Research and Innovation in Genome Editing (ARRIGE) Initiative (Jasanoff and Hurlbut 2018; Montoliu et al. 2018), as well as other entities, such as the World Health Organization (WHO), to commit to a human rights foundation for their deliberations. Rather than be distracted by the novel issues raised by GGE, it is crucial to consider how actual human lives and rights will be affected. Given the universal problems of social exclusion and unfair access to advantage, the implementation of GGE is sure to create human rights challenges that must be addressed for any agenda in ethics to make a real improvement in human lives.

Dual-use technologies, by their very nature, instill both optimism and trepidation. Development of CRISPR and other genome editing technologies may lead to treatments of previously incurable genetic diseases. Yet even with principled intentions, deployment of genome editing tools raises serious concerns, especially in the realm of GGE. As a faculty affiliate and a member of the Innovative Genomics Institute, we recognize and fundamentally support the imperative to evaluate and assess the ethical and societal ramifications of a technology alongside scientific advancements. As researchers, we believe we have an indispensable duty to guide the implementation of new technologies in ways that respect fundamental human rights. We fervently implore national and international bodies to integrate ethical and human rights considerations into their own evolving regulatory frameworks.

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