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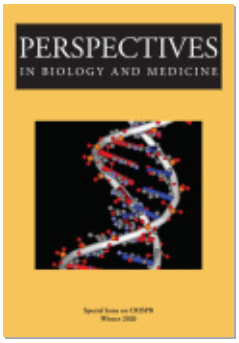


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# Who's Afraid of the Big Bad (Germline Editing) Wolf?

R. Alta Charo

**ABSTRACT** Germline genome editing has garnered dire predictions about its societal effects, but experience with other reproductive technologies should caution us about making extravagant claims. Amniocentesis was predicted to result in increased stigmatization of people born with Down syndrome, but in fact people with these conditions have been increasingly integrated into schools and workplaces. Artificial insemination by donor was predicted to result in women choosing to "optimize" their children, but in fact most women eschewed the offerings of the so-called "genius sperm bank," and when choosing among donors, have tended to look for those who most resemble their husbands and partners. IVF was predicted to cause parents to view children as commodities, but no such change has been evidenced. Preimplantation genetic diagnosis was predicted to become widespread and used for an ever-increasing range of conditions, including those unrelated to serious disease or shortened life span, but this has not happened either. Critics of germline genome editing have argued that even if it were safe and effective, it would inevitably be abused by prospective parents who wish to improve upon what is already predicted to be a healthy outcome, and that this practice would become sufficiently widespread among those able to afford it that we would be creating a new genetic caste system. Before developing policy around such predictions, it is important to learn from the past.

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The surprise announcement in November 2018 that a Chinese researcher had implanted and brought to term two gene-edited embryos, resulting in the birth of twin girls, had the effect of galvanizing a debate that goes back decades (Begley 2018; Evans 2002; Kevles 1985). Should we make heritable changes in our children's DNA? Until recently, this was hypothetical only, and the easy response was to say it is too uncertain and too unnecessary to be tolerated. Suddenly, however, the possibility that there might be real uses for mitochondrial DNA replacement or for germline editing has led to a more nuanced debate, ranging from calls to double-down on prohibiting this technology to discussions of how to permit it for a limited range of conditions, under strict oversight (Baltimore et al. 2015; NAS 2017; UNESCO 2015). Often lacking in this debate has been an effort to look back at debates surrounding earlier advances in reproductive technologies, most of which have been accompanied by fears of eugenics, the loss of human dignity, and the disruption of parent-child relationships. While these advances have each had pockets of abusive uses, they have been integrated into modern life without bringing about wholesale destruction of society.

A true prohibition of germline editing already exists in a number of countries, by virtue of their signatures to an international instrument. A number of international efforts focus on human rights, including the Universal Declaration of Human Rights, the International Covenant on Civil and Political Rights, the International Covenant on Economic, Social and Cultural Rights, the Convention on the Rights of the Child, the Convention for the Protection of Human Rights and Fundamental Freedoms, and the European Social Charter. But it is the 1997 Council of Europe's Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine, better known as the Oviedo Convention, that was written specifically to address the intersection of human rights and biomedical developments, and aimed to protect the "dignity and identity of all human beings" (Council of Europe 1997).

Article 13 reads: "An intervention seeking to modify the human genome may only be undertaken for preventive, diagnostic or therapeutic purposes and *only if its aim is not to introduce any modification in the genome of any descendants*" (emphasis added). In other words, even if done with the best of intentions, to ward off devastating—even lethal—conditions, the Convention admits of no alterations that are meant to affect descendants, though this position has not been without its critics (Council of Europe 2017; Cyngell, Douglas, and Savulescu 2017; De Wert et al. 2018; Hasson 2018).

Debates around germline editing focus on multiple concerns. With regard to physical harm to individuals living in the future, this involves a risk-benefit analysis that is complicated by the multigenerational potential of the change (Baylis 2018; Rubeis and Steger 2018). This alone introduces questions about the stability and durability of the alteration, its effect under future (presumably different) environments, and the ever-increasing number of generations between the person affected and the person initially giving consent.

A different objection goes directly to how we understand autonomy. As noted in the July 2018 report by the UK Nuffield Council, one might argue that "choosing someone else's genetic endowment . . . offends against the essential dignity and nature of the person as a free and independent human being." In essence, this argument is that germline editing interferes with a child's "right to an open future" (Feinberg 1980, 1992). But one response has been not only that parents make many momentous decisions affecting their children's lives, but that the acceptability of parental choices rests on whether they serve to expand or narrow a child's prospects, and whether the changes were made for the welfare of the future child, such as preventing serious disease and disability (NAS 2017; Nuffield Council 2018). Of course, it should be noted that many in the deaf community and the community of little people would not define those conditions as disabilities, but rather as varieties of the human community. But this is the exception, and other groups with shared disabilities have not refused the designation, although they often argue the degree of impairment is as much a function of social and physical context as it is anything intrinsic to the body.

Other concerns about germline editing revolve around fear that it will lead to intolerance of imperfection, turning children into commodities rather than the subjects of parental love, and that it will result in stigmatization of those who are disabled (Thiessen 2018). These concerns are not unfamiliar. They have been raised repeatedly with each new advance in reproductive technologies, whether prenatal screening, gamete donation, IVF, surrogacy, preimplantation diagnosis, and cloning. Germline editing is simply the latest rehearsal of what are fundamentally the same concerns around intolerance for diversity or imperfection.

By the 1970s, amniocentesis had entered clinical care and was used to screen early second trimester fetuses for chromosomal abnormalities such as triploidy associated with Down syndrome (Cowan 1993). The prospect of abortion being used to eliminate the birth of children with this and other chromosomal conditions sparked widespread discussion about the value that persons with disabilities find in their own lives, about the prospect of nongovernmental eugenics (even absent government influence, a pattern of common decision-making among individuals), and about whether the ability to avoid the birth of children with these conditions would affect the way parents regard all children and lead to "commodification" of children that undermined their status as a gift or a blessing. But while the rate of births with Down syndrome has been dramatically affected in some places, the overall number of these births has continued to be substantial and, if anything, acceptance of people with Down's has only increased in the intervening years (Guralnick, Connor, and Hammond 1995; Hocutt 1996; Kasari et al. 1999; Mansfield, Hopfer, and Marteau 1999; Natoli et al. 2012).

The 1980s saw the rising use of artificial insemination, with its associated public fears that women would flock toward the "Genius Bank" for "superior sperm." This did not happen, and reportedly no more than a few dozen children were born from this source. Surveys show that most people simply want donors

who will resemble the nongenetic rearing parent (Klock and Maier 1991; Nielsen, Pedersen, and Lauritsen 1995; Nijs 1982; Scheib, Raboy, and Shaver 1998).

That decade was also the era of surrogate motherhood and in vitro fertilization, two reproductive techniques that were, again, predicted to undermine parent-child relationships. In vitro fertilization (IVF), by which eggs are fertilized in a laboratory and grown until ready for transfer to a woman who will gestate them until birth, was viewed as unnatural, yet parent-child relations have not in fact been harmed. While surrogacy has had a problematic history, it is due not to the loss of parental love but rather to the effects of wealth inequality, which has led some to worry about exploitation of low-income women, in the US and elsewhere (Markens 2007). This is particularly true when IVF is used in conjunction with surrogacy, as in these cases the rearing couple uses their own gametes and the pregnant woman has no genetic relationship with the child she bears, so her own physical and genetic characteristics may be of little concern to the rearing couple (Johnson v Calvert, 851 P.2d 776 (Cal. 1993)).

The one area where problems have seemed most acute is egg donation. An overly deterministic view of genetics led some rearing couples to seek egg donors who had high standardized test scores or were students at elite universities, with exaggerated payments as inducements. While there is little evidence of long-term physical harm from ovulation stimulation, especially when done only once, it still poses some risk to healthy young women. But here, again, despite many articles discussing the phenomenon, evidence of the practice has been anecdotal, and it is not clear how widespread it became (Almeling 2007).

In the 1990s, the next development to stir controversy was preimplantation genetic diagnosis, whereby in vitro embryos could be biopsied and those with known deleterious mutations left unused. Debates surrounding appropriate use of PGD focused on two fears. First, there was concern that parents would use the technique for ever more trivial reasons and finally push society toward the commodification of children and intolerance of imperfection that had been predicted with each of the previous reproductive technology advances (Greely 2016). Here too, however, experience showed that the expense and inconvenience of IVF, plus the limited range of conditions that could be reliably identified, meant that its use was largely restricted to serious or lethal conditions And the Americans with Disabilities Act (ADA) led to tremendous progress toward making workplaces, homes, and public facilities accessible so that those with disabilities would no longer be isolated from the wider community.

The second fear, however, was that it might be used for sex selection, which in turn was viewed by some as reification of sex differences that had undergirded centuries of discrimination against girls and women. Sex selection had been possible with amniocentesis since the 1970s, but the prospect of selective abortion deterred many people in the US. In PGD, however, there was the chance to do sex selection without an abortion. But again, only very highly motivated people have

been willing to undergo the expense and inconvenience of IVF simply to ensure the birth of a child of one sex or the other (Macklin 2010; Steinbock 2002).

Later in the 1990s, the prospect of human cloning led to a flurry of efforts to ban what was seen as an immoral or dangerous procedure. But the public showed little appetite to pursue it for human purposes, despite some high profile (and rather silly) claims about its success—all of which proved to be fraudulent. Nonetheless, both the Oviedo Convention and a host of state laws in the US and national policies abroad have adopted criminal penalties for attempting this.

As we entered the 21st century, attention turned to mitochondrial replacement, a technique that would be useful for women whose eggs carried mitochondrial DNA known to cause a wide variety of health problems. PGD provided no solution, so for those who wished to maintain a genetic connection to their offspring, one solution was to use donated, healthy mitochondria. A number of attempts were made over the course of two decades, beginning in 1996 (Wolf, Mitalipov, and Mitalipov 2015). By 2016, several dozen children around the world had been born following conception using this technique, though with varying (and arguably inadequate) attention to longterm followup and transparency in data reporting and sharing (IOM 2016; Kula 2016).

Mitochondrial replacement entered the realm of transgenerational genetic modification, as the altered eggs would result in offspring who, if they were girls, would carry that donated mitochondrial DNA in their own eggs and pass it down to the next generation, and the next, and the next. The Oviedo Convention appeared to prohibit this. Critics worried that this would become a sought-after technology for older women, including those with no known mitochondrial disease, in the hope it would enhance their fertility. It is too early to know if this dire prediction will come true, but based on past experience, the risks and discomfort (to say nothing of the expense) associated with this technology will limit its users to those with a compelling need. In addition, a recent study suggests the technique is not particularly successful at increasing the chance of conception for older women (Mazur et al, 2019). For the moment, such a procedure has been rendered de facto illegal in the US, by virtue of a federal budgetary provision that precludes FDA review of a request to begin clinical trials involving the technique (Kaiser 2019), and the UK remains the only country with explicit regulations governing permitted indications (HFEA 2015).

In sum, as we approach the end of the first quarter-century of the new millennium, there has been a half century of experience with new technologies predicted to alter human relations and give people a power that they would inevitably abuse, but which did not in fact result in these dystopian futures. Despite this, the same predictions are made about germline editing.

The debates around germline editing continue, but the science remains in preliminary stages, and there is still time to take a close look at why and how these earlier reproductive technologies spread, what their limiting factors were, and how such factors might help in formulating better predictions for the range

and scale of use one might expect for germline editing. For example, IVF was originally developed to circumvent blocked fallopian tubes, but its use rapidly expanded to encompass idiopathic infertility, male sub-fecundity (in conjunction with intracytoplasmic sperm injection), egg donation, and gestational surrogacy. But given the expense, discomfort, and risks of IVF, it did not expand to populations able to conceive through intercourse without significant fear of passing on a serious genetic condition but who (as was feared and predicted at the time) would want to use PGD to screen for conditions that do not seriously impair health. At most, there was some small uptake that involved screening for later-onset cancers. How much this has been due to the lack of motivating reasons to undergo IVF versus the limits of PGD screening would be quite relevant if one wished to extrapolate to probable patterns of germline use.

Another worthwhile effort would be to calculate the number of people who might be interested in germline editing. Primarily this would be the very small number of people for whom PGD is not an option, such as those couples where one parent is homozygous for a dominant mutation such as Huntington's. Secondarily it might be couples for whom the number of available embryos following PGD is quite small. Who are these people, and are their numbers (and their marital patterns) sufficient to raise the spectre of exacerbating inequities or creating a genetically superior caste of society, as is feared by some? A peculiar aspect of the germline editing debate has been the assertion, on the one hand, that it could be banned, as very few people actually need it, and the assertion, on the other hand, that it will become sufficiently popular to have a global effect on humanity's own genome.

In the debates surrounding the use of genome editing for germline alteration, one of the frequently raised concerns is its possible effect on human evolution. Given the need to do IVF, it would seem unlikely to become a sufficiently prominent part of human reproduction to have any evolutionary effects in the foreseeable future, even if its substantial technical, regulatory, logistical, and economic barriers could be overcome. More likely to become a part of our lives would be genome editing that lacks transgenerational effects, such as somatic editing at the fetal or postnatal stages, or—even more limited in its effects—epigenetic editing for transient alterations. It is for this reason that the ongoing effort by the World Health Organization to develop guidance for global governance of genome editing will focus not only on germline changes but on the broader range of uses (WHO 2018). More distantly related to the subject of this essay, genome editing may become a potent addition to the already extensive arsenal of tools available to create—and defend against—biological weapons.

As germline editing moves from science fiction to laboratory to (perhaps) the clinic, good governance will always begin with good facts.

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