Setting ethical limits on human gene editing after the fall of the somatic/germline barrier

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The ethical debate about what is now called human gene editing (HGE) has gone on for more than 50 y. For nearly that entire time, there has been consensus that a moral divide exists between somatic and germline HGE. Conceptualizing this divide as a barrier on a slippery slope, in this paper, I first describe the slope, what makes it slippery, and describe strong barriers that arrest the slippage down to the dystopian bottom of pervasive eugenic enhancement. I then show how the somatic/germline barrier in the debate has been weakened to the level of ineffectiveness, with no replacement below. I examine a number of possible barriers on the slope below the somatic/germline barrier, most of which lack sufficient strength. With the exception of the minority of people in the HGE debate who see the eugenic society as utopia, the majority will need a barrier on the slope to stop the slide to dystopia.

human gene editing | bioethics | germline | slippery slope

Since the 1950s, there has been an ethical debate about what we would now call "human gene editing" (HGE) (1). In the 1950s, after realization of the connection of mainstream eugenics to the Holocaust, the "reform" eugenics movement concluded that desirable genetic capacities were not clustered in races, ethnicities, or social classes but could be found in all groups. To improve the species, the persons with better qualities should have more children and those with lesser qualities should have fewer (2).

The developing understanding of genes as chemicals made eugenicists consider that perhaps genes could be directly manipulated. Distinguished biologist Robert Sinsheimer wrote during this era that the new technologies allowed for "a new eugenics...The old eugenics would have required a continual selection for breeding of the fit, and a culling of the unfit. The new eugenics would permit in principle the conversion of all of the unfit to the highest genetic level...for we should have the potential to create new genes and new qualities yet undreamed" in the human species (2).

By the early 1970s, scientists began to imagine changing the genes in an existing person, something that no eugenicist focused on social schemes could have imagined, or even have wanted, as their goal was always to improve the species, not an individual. Beginning with the invention of human somatic "gene therapy," scientists, philosophers, theologians, and other participants in the debate have used the somatic/germline distinction as a moral limit. Somatic means changing genes in some of the cells of an existing person in a way that does not impact their reproductive cells, and germline means changing the genes in someone's offspring and, ultimately and in a small way, the human species. By creating a line that scientists would not cross, less controversial research like somatic gene therapy continued apace.

I will argue that currently, despite appearances, in the mainstream US and UK bioethical debate that has the greatest influence over what actually happens with science policy, the somatic/germline distinction has lost its power. For example, despite the uproar over He Jianqui's facilitation of the gestation and birth of germline modified children in China, the leadership of the Second International Summit on HGE implicitly agreed with him that it is in principle acceptable to engage in germline intervention, as long as it is safe and human subjects protections are followed (3). Indeed, a commission of the National Academy of Medicine, National Academy of Science, and the Royal Society recently developed a "translational pathway" for the "responsible use" of germline applications (4).

There is a structure to debates such as this. Understanding this structure will help us understand what led to the weakening of the somatic/germline distinction and what limits, if any, will be advocated in the future debate. I begin with a brief primer on these moral distinctions in the debate and then turn to the history of the somatic/germline distinction. I then explain what has weakened it to the point of being nearly an illusion. Furthermore, for those who do not advocate total freedom in reproduction, I discuss possible future limits on HGE that could be drawn. This article is built on ideas from my recently published book, which justifies these points in more detail (5).

Moral Limits as Barriers on a Slippery Slope

The best way to understand the debate about germline HGE is a sociological version of the slippery slope metaphor (6–8). A slippery slope is a metaphorical slope with the most meritorious position at the top, and at the bottom is the position that is maximally objectionable from the view of the top. Stepping onto the top of the slope at option A, it is more likely in the future that we will select the currently objectionable somewhat downslope option of B. If we get to B, we are more likely to select an even more objectionable option of C further down the slope. The morally worthy decision at the top changes the social and argumentative context of the next decision, making the more objectionable choice below more likely. Eventually, we are at the bottom of the slope, which we had no intention of reaching when we started onto the slope. For example, such an argument about euthanasia would be that once euthanizing the terminally ill becomes normalized (step A), it is more likely that people will accept euthanizing those who just do not want to live any more (step B), which makes it more likely that people will accept euthanizing those who do not contribute to society (step C).

Stepping onto the top of the HGE slope in the early 1970s at somatic gene therapy, the position at the very bottom was that of the eugenists who wanted to perfect the species by making us

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more genetically intelligent, musical, or virtuous. In these debates, the bottom is portrayed as a society where most reproduction takes place through germline modification and humans are designed by others to fulfill specific goals. Metaphorically, the conservatives in the HGE debate see the bottom of the slope as represented by the 1931 novel *Brave New World* by Aldous Huxley, which depicted a society that violates bodily and spiritual purity due to the ultimately dehumanizing design of people, resulting in humans being more object-like. The liberals see the bottom as represented by the 1997 movie *Gattaca*, where children's genetic qualities are selected in line with a rigid genetic hierarchy, resulting in strong social and economic inequality.

Of course, there are some debaters who want to get to the bottom of the slope as fast as possible, who want a world of improved humans, and who reject the dystopian assumptions of the critics. I acknowledge that these perspectives exist in the HGE debate, but the dominant discourse is about what the limits of the technology should be.

How Does a Slope Slip?

Motivated to relieve the suffering of existing people with devastating genetic diseases, in the early 1970s, skeptics stepped onto the slope at somatic gene therapy, assured it would not slip to the bottom. What then caused the debate to slip downslope? To understand how a slope may be slippery, we have to understand its terrain. The terrain is defined by what is morally relevant about the position on the slope, such as: what is morally relevant about the act of somatic gene therapy? Which vector delivered the new gene was not morally relevant. On the other hand, the origins of the HGE debate in the eugenics movement has meant that the targeted phenotypic trait was morally relevant. The acts on the terrain of the slope have been ordered so that "disease" traits are near the top and "enhancement" traits are near the bottom. The other feature of the terrain has been target. By target, I mean either "an existing person" or "future generations." The terrain of the slope—the different locations—is therefore made up of combinations of traits and target, in order from the most to least acceptable to modify. Diseases in an existing person are at the top, intelligence in the human species is at the bottom.

So, how does a debate slip one unit down the slope? Steps down slippery slopes are the result of an absence of a sharp line between cases (9) that I will simply describe here as similarity between the steps. Basic cognitive processes lead to this slippage (10). To foreshadow relevant instances of similarity causing slippage, think about the similarity between Huntington's and early-onset Alzheimer's. If the metric is relieving suffering, the slope between these two diseases will be very slippery. After all, how would you rank these diseases on one continuum of suffering?

It is then similarity between two locations on the slope that produces the grease that allows the limit to HGE to slip downslope. However, similar by what standard? A 1974 Ford Pinto and a new Ferrari are similar if the standard is driving from point A to point B. They are quite dissimilar if the standard is price. In debates about ethics, the standard is moral values, and a value is defined here as what we strive for (11). Therefore, two points on the HGE slope can only be made similar through this slippery slope process if they are justified with the same moral value. For example, using HGE for sickle cell disease and HGE for early-onset Alzheimer's can be made similar or the same if both are only justified by the value of the relief of suffering. They are not similar if the standard is age of onset.

The final piece of my metaphor is the barrier on the slippery slope. The entire ethical debate about HGE is about these barriers, and whether the consensus in the moral limit slips down the slope depends on whether the barriers hold. Many bioethical debates that try to influence policy are organized as barriers on slippery slopes (e.g., abortion, chimeric life-forms, embryo research, euthanasia). Philosopher John Harris writes that "slopes are only slippery if they catch us unawares and we have strayed on to them inadequately equipped" (8), and the equipment is "easily enforceable bright-line rules" (9). Buchanan et al., in their influential book on HGE, call these barriers "moral firebreaks" (12). Barriers are typically not set at some meeting or by decree but rather develop as a consensus among those debating in the academic literature.

The final question is what makes a strong barrier. A strong barrier separates two steps on the slope that cannot be made similar. To anticipate a later discussion, the somatic/germline barrier has been very strong because on one side has been "an existing individual" and on the other "their offspring or the species." Individual and offspring will always be considered dissimilar.

For a barrier to hold, this design of separating the dissimilar must be strong. However, a value change in the debate can overcome a barrier by redefining what is relevant about the act on the terrain, making the acts on the two sides not dissimilar but similar. For example, if the values change so that the difference between an individual and the species is irrelevant, then the barrier would fall. In sum, in this paper I explain how acts on the two sides of the somatic/germline barrier were made similar in the debate, thus weakening the barrier, and show the challenges of the debate reaching consensus on any barriers further downslope.

History of the Barriers in the HGE Debate

Reform eugenicists from the 1950s to the 1970s mixed disease and enhancement in their proposals. For example, H. Bentley Glass, who would later be president of American Academy for the Advancement of Science, wrote in 1965 that he was looking to create the "good man," who would have "freedom from gross physical or mental defects, sound health, high intelligence, general adaptability, integrity of character, and nobility of spirit" (13).

In this era, the scientific community felt threatened due to criticism on a number of fronts (14), and the idea that scientists would decide the future design of the human species became especially controversial. As scientist Bernard Davis wrote in *Science* in 1970, discussions about HGE "have tended toward exuberant, Promethean predications of unlimited control and have led the public to expect the blueprinting of human personalities." The "exaggeration of the dangers from genetics will inevitably contribute to an already distorted public view, which increasingly blames science for our problems and ignores its contributions to our welfare. Indeed, irresponsible hyperbole on the genetic issue has already influenced the funding of research" (15).

The first barrier on the slope developed at the spot between disease and enhancement and came from both a desire to calm the public outcry and a strong dose of scientific realism about the ability to make enhancements. While changing a known monogenic disease was at least plausible, Davis argued for the barrier when he wrote that most geneticists had "more restrained second thoughts" about the possibility of engineering the polygenic behavioral traits that motivated the eugenicists (15). Scientists began to write that monogenic diseases are upslope of the newly forming barrier and thus morally acceptable to modify. Polygenic enhancements like "the blueprinting of human personalities" were in the forbidden zone downslope of the barrier.

In this era, the somatic/germline barrier also developed, which would further distinguish the emerging genetic scientists from the controversial eugenicists. A number of key articles and debates between 1969 and 1972 developed the idea of this barrier (1). For example, in a 1971 debate between HGE pioneer W. French Anderson and theologian Paul Ramsey, Anderson argued against the relevance of a somatic/germline barrier, stating that any genetic modification could be "therapy." Ramsey

responded that Anderson had described "gene therapy upon an as yet unconceived individual, upon germinal matter, [and] the gametes." However, to Ramsey, "therapy" only applied to existing people, and claiming to therapeutically modify the species is actually scientists trying to eugenically design humanity (16). Ramsey's view that individual and species should be distinct eventually won, the somatic/germline barrier was accepted, and Ramsey became an advocate of (only) somatic gene therapy near the top of the slope.

A barrier is solidified by writers assuming it is in force, and scientists did so by only focusing on developing somatic gene therapy, while the ethical debate turned to the question of when it was safe enough to engage in somatic gene therapy trials (17). By the 1980s the disease/enhancement and somatic/germline were the only barriers (18, 19)—barriers that structure essentially all debate to this day.

The Design Strength of the Original Barriers

To recap, a barrier is structurally strong if there is a strong dissimilarity between the acts on the immediate upslope acceptable side and the immediate downslope unacceptable side. In the early years of the disease/enhancement barrier, the very limited knowledge of human genetics meant that, unlike later years, "disease" (e.g., cystic fibrosis) and "enhancement" (e.g., intelligence) were radically dissimilar. This was a time before genetic tests, the Human Genome Project, and knowledge of epigenetics. Genetic "diseases" were only those traits that were easily observable in an existing person and were clearly different from normal human variation. It is easy to distinguish the traits of sickle cell and intelligence.

Later increases in our biological understanding made the concept of genetic disease, and the distinction from enhancements, less clear. For example, in the late 1980s, it was noted that genetic research had begun to identify "the genetic roots of an increasing range of predispositions and susceptibilities to disease" and diseases "that do not manifest themselves clinically until late in life" (20). Is reducing susceptibility to a disease creating an enhancement? Is deafness normal human variation or a disease? In my terms, there is extreme similarity between acts that were on different sides of the barrier, as no one can create a moral distinction between sickle cell and propensity to cancer at age 80. Since the weakness of this barrier is well established (19), I will focus on the somatic/germline barrier for the rest of this article.

The somatic/germline barrier was originally unassailable. There was no way to make acts on the two sides similar, because the dominant values defined the acts on the two sides by the target of the modification. The act on the upslope, acceptable side concerned individuals who could be met and who could actually be asked if they wanted to be modified. They existed in the present. In contrast, on the downslope side of the barrier was the human species, which was an abstraction that could never be met and could obviously not consent. Any change was in the future. Defined in this way, there was no way to make the terrain on the two sides similar and the barrier was strong.

Influential values in the debate made this barrier strong by reinforcing that the acts on the two sides were defined by having different targets. A universally held value that supported the barrier was nonmaleficence (avoiding harm). Nonmaleficence supported the somatic applications upslope, which were the least risky. If a mistake were made with somatic HGE, the impact of that mistake would end with the death of the modified person. However, with germline, below the barrier, a mistake could be handed down to offspring and to the broader human population. The value of humility and avoiding its antonym hubris also supported the barrier because the acts on individuals above the barrier were cautious, whereas below the barrier, it was hubristic to think that mere humans had the wisdom to redesign ourselves.

Most importantly, acts above the barrier were supported—and acts below the barrier condemned—by the value of respecting "nature" or "God's will" in not modifying the design of the species. Above the barrier, with somatic, nature or God's creation was not being redesigned, humans were simply modifying existing nature as they have always done with medicine and technology. In contrast, those arguing for somatic HGE, such as the theologians of the era, criticized the discredited values held by eugenicists below the barrier, like that of geneticist Theodosius Dobzhansky, who wrote that "Evolution need no longer be a destiny imposed from without; it may conceivably be controlled by man, in accordance with his wisdom and values" (21). These values defined the proposed acts and, so defined, made clear distinctions between the two sides of the barrier. The values supporting this barrier were originally dominant, until a shift in participants brought in different values.

Value Change Damages the Somatic/Germline Barrier

Before the early 1980s the audience for the debate was the public and scientists. After this point, the debate increasingly became input for government policy at NIH and other policy venues (22). Values that could not be portrayed as universally held by all of the citizens, such as the values promoted by theologians, were decreasingly acceptable as input for policy. This led to the rise of a new profession of "bioethicists" who tended to only use four purportedly universally held public values: beneficence (benefitting others), nonmaleficence (avoiding harm), respect for autonomy, and justice. Other values, such as "following nature" or "God's will," slowly became marginalized in these debates (1).

Beginning in the mid-1980s, participants in the debate began to claim that the values of beneficence and nonmaleficence forwarded by the bioethics profession defined and supported acts on both sides of the somatic/germline barrier. If other values are not considered, and if acts on both sides of the somatic/germline barrier are beneficial and safe (avoiding harm), all that is needed is the disease/enhancement barrier, which was still viable at the time. As bioethicist John Fletcher and scientist W. French Anderson wrote, "searches for cure and prevention of genetic disorders by germ-line therapy arise from principles of beneficence and nonmaleficence, which create imperatives to relieve and prevent basic causes of human suffering. It follows from this ethical imperative that society ought not to draw a moral line between intentional germ-line therapy and somatic cell therapy...In our view, a moral line should be drawn between... disorders with the greatest magnitude of suffering, pain, and early death—and efforts at 'enhancement' by either mode of therapy" (23).

Another new value promoted by bioethicists was respect for autonomy. The idea that people had bodily autonomy was not an established value at the time the barrier was built. When the barrier was created, doctors did not have to ask your consent for procedures and might not even tell you had a disease (24). Abortion was illegal in most of the United States, and the reasoning of the *Roe v. Wade* decision that used respect for autonomy to structure debates about reproduction would not be handed down until 1973.

During the 1980s, the abortion rights movement expanded to include the idea that women have the autonomous right to make decisions about not only their fetuses but also zygotes and embryos. Concurrently, many participants in the HGE debate started to reflect on how one would actually produce a germline change and realized it would require modifying reproductive cells, zygotes, or embryos. Therefore, they wanted the acts below the barrier to be defined as "reproduction." If the terrain is defined by the value of respect for autonomy, then one has the autonomous right to decide whether to be somatically modified and the autonomous right to engage in germline HGE for his or her offspring. For example, John Robertson claimed that people

have a fundamental autonomy right to germline HGE because "gene therapy on the embryo is closely tied to procreative choice...The U.S. Constitution...gives the parent the right to provide his or her children and their descendants with a healthy genome...The right to procreate includes a right to practice negative eugenics – to deselect harmful characteristics from future generations" (25). If beneficence, nonmaleficence, and respect for autonomy are the primary values in the debate, the acts upslope and downslope of the somatic/germline barrier are the same, and thus the debate will topple the barrier. While there was now a group in the debate ready to fell the barrier, and had identified how to do it, the barrier remained standing in its weakened form because scientists still could not see how to actually conduct germline HGE.

Individuals below the Barrier

The greatest damage to the barrier came when new technologies defined some of the acts below the germline barrier as actually impacting individuals, not the species. Recall that this barrier was built to draw a boundary with the eugenists, who were primarily interested in improving the human species, so below the barrier was the species. As technology improved, what is now obvious came into view, which is that to change a species, you must first change individuals. The moral view of the acts below the barrier began to focus on the changed individual who would be produced and largely ignored any influence that the individual would subsequently produce on the species. If there are individuals on both sides, this is a similarity, which will further weaken the barrier.

The first act below the barrier impacting an individual was the hypothetical future patient. For example, LeRoy Walters was the bioethicist who was the chair of the committee at the NIH that regulated trials of HGE. He extrapolated from the beneficent relief of suffering from disease for an existing individual on the somatic side of the barrier to a future individual on the germline side, arguing that "Affected offspring could presumably be treated by means of somatic-cell gene therapy in each succeeding generation, but some phenotypically cured patients would probably consider it more efficient to prevent the transmission of specific malfunctioning genes to their offspring, if the option were available" (26).

Similarly, somatic gene therapy pioneer Theodore Friedmann wrote that "it has been suggested that the need for efficient disease control or the need to prevent damage early in development or in inaccessible cells may eventually justify germ line therapy" (17). For example, somatic modification of the cells in an existing person's brain is not easy, because the cells are inaccessible. However, a modified embryo would develop the genetically modified brain. There was now a person with a genetic disease upslope requiring somatic modification, and one downslope who requires germline invention to prevent the disease in the first place. If the only values are beneficence and nonmaleficence, these acts on individuals are the same, so Walters and Friedmann argue for taking down the barrier.

Far more consequential for future debate was that a different technology was now placing actual babies below the barrier. It is testimony to the incredible strength of the barrier that, at first, few saw the implications. In 1978, in vitro fertilization was invented, which did not influence the genetic qualities of the offspring. However, it was discovered in 1989 that the genetic qualities of those embryos could be evaluated using what is now called preimplantation genetic diagnosis (PGD). With PGD, a number of embryos are created and all are tested, and those with desirable genetic qualities are gestated and the undesirable discarded. This was, in effect, germline selection (not modification) of the traits of a baby and ultimately a (very small) influence on the species as the eugenicists would have desired. It changed the germline of the baby compared to what it otherwise would have been.

A few participants in the debate realized that PGD produced a baby on the slope below the germline barrier, and we again had the similar individual with a potential disease both upslope and downslope. Bioethicist LeRoy Walters predicted a scenario that would, in my terms, produce almost perfect similarity of acts on both sides of the germline barrier. A couple would like to use PGD but could not because they are opposed to destroying embryos, or are not capable of producing embryos that do not have disease. If germline modification of their embryos was performed for this couple, the goal would be to produce an individual—a healthy baby—not influence the species: "in both of these scenarios, germ-line transmission would be a foreseeable but unintended side effect of a therapeutic procedure intended primarily to cure disease in an (embryonic) individual" (27). These insights had little impact on the HGE debate because PGD was perceived to be a part of the abortion debate. As PGD became more commonplace, and could identify more traits, the stage was set for later weakening the barrier.

The Invention of CRISPR

When CRISPR was invented in the 2010s, the somatic/germline barrier sat in its dilapidated form on the slope but with no one yet motivated to push it over, because it appeared at the time that germline modification was always going to be impossible. However, the barrier was there, providing the moral categories for the reenergized post-CRISPR HGE debate.

After it became clear that some scientists were trying to use CRISPR to modify human embryos in the laboratory, many scientific groups released position papers on HGE, mostly defending the somatic/germline barrier using the value of nonmaleficence (safety). For example, In August 2015, the American Society for Gene and Cell Therapy and the Japan Society of Gene Therapy released a statement that the "safety and ethical concerns" about germline HGE are "sufficiently serious to support a strong stance against gene editing in, or gene modification of, human cells to generate viable human zygotes with heritable germ-line modifications" (28). A group of somatic gene therapy researchers wrote that "patient safety is paramount among the arguments against modifying the human germline" because it "could have unpredictable effects on future generations" (29).

The National Academies Report Exemplifies the Weakened Barrier. The National Academies of Science, Engineering, and Medicine convened a committee to study HGE in 2015. (It is important for transparency to report that I was a member of the committee.) It is critical to point out that the committee started with the accurate assumption that the barrier cannot be supported only by nonmaleficence, because if germline HGE becomes safe, then there is no need for the barrier. Furthermore, it appeared that CRISPR would soon make germline modification safe. Crystalizing the mainstream debate and only using the values promoted by the bioethics profession, the committee advocated taking down the barrier by emphasizing the value of (reproductive) autonomy, which subtly redefined the acts on the two sides of the barrier as the same.

The committee used two arguments made by Walters 25 y earlier that made acts upslope and downslope substantively identical. In the first, a hypothetical couple using PGD for a disease like sickle cell was described as upslope in the acceptable zone. Located downslope of the barrier in the traditionally unacceptable zone was the hypothetical couple who is almost exactly like the upslope couple but cannot use PGD because all of the embryos they produce would express the disease, or the woman produces few eggs (30). They would want to edit their embryo.

In other words, the couples standing upslope and downslope of the somatic/germline barrier are the same. To create a barrier between the couples, someone would have had to come up with values that focus on the difference. However, I cannot imagine a value that distinguishes women who produce many eggs from those who produce few or distinguishes a couple that produces some embryos without sickle cell vs. a couple that produces no embryos without sickle cell. The section of the report concludes that "In all of these situations, if it were safe and efficient to use heritable genome editing (e.g., in gamete progenitors) to correct the mutation, this alternative might be preferred by prospective parents who otherwise would be considering PGD" (30). If the only value is respect for autonomy, prospective parents can choose between PGD and HGE, and there should be no barrier.

In the second argument, there were different couples on either side of the barrier. The report states that another reason to take down the barrier is that PGD requires "discarding affected embryos, which some find unacceptable" (30). Therefore, upslope is the couple who are carriers of sickle cell who can use PGD because they do not place high value on embryos, and downslope is a couple who wants to use germline modification because they cannot use PGD due to the high value they place on embryos. Again, what value would justify treating these two couples differently? It would be a value like religious discrimination, which is obviously not supported in this community. It was not that the Committee shared this concern with embryonic life—there is an entire chapter advocating experimenting on and ultimately destroying embryos. Rather, the concern about embryos is justified with the value of respect for autonomy because there are couples who believe that embryos have high value. The barrier should fall because of extreme similarity between the acts on the two sides of the barrier, which is only possible if the only value is respect for autonomy.

To replace the somatic/germline barrier, the National Academies report proposes a version of the disease/enhancement barrier where germline modification would be restricted to "preventing a serious disease or condition" (30). My interpretation of the committee's barrier is that it certainly cannot hold in the long run because "serious" is very slippery. However, the Committee thought it would be relevant when the only traits being considered for modification were the consensual diseases for which people sought out PGD, like sickle cell. The recent National Academies translational pathway relies even more heavily on being able to distinguish "serious" diseases (4).

The 2017 National Academies report served as a capstone on the debate. Faced with legitimate scientists who, for the first time, actually wanted to conduct germline HGE, they found that the dominant values in the public bioethical debate cannot support the somatic/germline barrier.

Possible Barriers below the Somatic/Germline

The somatic/germline barrier still sits on the slope, in dilapidated form. That is, people still use the term "germline" in ethics, but that is largely because the value of nonmaleficence (safety) at present coincides with the location of the barrier. If technology improves and germline HGE becomes safe, then acts on both sides of the barrier will be the same (equally safe), and the barrier will immediately fall. Scientists and bioethicists will endorse moving forward with clinical trials.

It is important to note that if the public's values were to be incorporated into the debate, as has been proposed (22, 31, 32), it is quite plausible that the somatic/germline barrier would be supported. For example, the public is likely to support the value of following nature or God's will (33). Moreover, there are a few more values that are used in continental Europe that bolster the somatic/germline barrier used there (34, 35).

In our search for a strong barrier on the slope below the somatic/germline, we first need to determine our values. Are we going to pursue preserving nature as it is, or reproductive autonomy, or beneficence, or something else? Our value will tell us what we should even pay attention to in an act of HGE—what the terrain of the slope is made of. For example, if we are only using beneficence, the only thing that matters about an act is whether it would reduce suffering, and concepts like somatic and germline would be irrelevant.

Once our value tells us what we should focus upon with the act, we need to identify an act just upslope and an act just downslope of our barrier that cannot be made the same. I have called this "design strength," and the somatic/germline barrier originally had great design strength. Individual and species could not be made the same, although the creation of PGD revealed some limitations to the original design, creating some slipperiness around the barrier.

Now armed with our understanding of how barriers work, I ask what possible barriers exist between the somatic/germline barrier and Gattaca or the Brave New World at the bottom of the slope. I focus on identifying design strength, looking for barriers for which a nonslippery distinction can even be made, to show how few possible barriers there are. Whether values can support these barriers is a separate question.

The "Scientific Reality" Barrier. We must immediately dispense with a barrier that many find attractive and that I call the "scientific reality" barrier. This is knocked over as we understand the acts on both sides and immediately rebuilt downslope at the limit of our understanding, essentially sliding down the slope as our knowledge accumulates. The argument is that technology X will always be impossible, so X can be the location of the barrier on the slope, putting scientifically possible above the barrier and scientifically impossible below. For example, we could say it will always be impossible to modify polygenic personality traits, so that act can serve as a natural barrier in the debate.

Perhaps X will always be impossible. However, I think that the history of scientific progress suggests that it is not wise to bet against the growth of human knowledge and that the impossible has a tendency to become the possible. CRISPR itself is a case in point. With each increase in our knowledge, the terrain directly below the barrier is redefined from impossible to possible, resulting in similarity across the barrier, and the barrier falls and is rebuilt further downslope at the limit of our knowledge. This is then not really a barrier.

The Goals of Medicine Barrier. Since it has long been thought of as impossible to come up with an objective definition of disease and enhancement, some have advocated a barrier located at the goals of medicine, letting the current medical profession define disease. This is the "professional domain account" of disease, where "'treatments" are any interventions that the professional standards of care endorse, while "enhancements" are any interventions that the professions declare to be "beyond their purview" (36).

This barrier would be far into the enhancement part of the slope because the medical profession already engages in human enhancement with "wish fulfilling medicine" (37) such as plastic surgery and prescribing drugs that focus attention. Therefore, if doctors prescribe pills for mental focus, genetic modification for mental focus would be the same and upslope of this barrier. More critically, the goals of medicine are in flux, which would continuously redefine the terrain around the barrier, making it slippery. Indeed, this shifting of the goals of medicine to cover more and more human experiences is so pervasive that medical sociologists have a term for it: medicalization (38). How far down the slope the profession might reach is suggested by the 1947 statement of the World Health Organization that defined health as "a state of complete physical, mental and social well being and not merely the absence of disease or infirmity" (39). This barrier would not hold.

The Boundary of Humanity Barrier. To see a possible barrier with a very strong design based on a strong dissimilarity, we go many decades into the future and near the bottom of the slope. Eric Lander, in an editorial in the *New England Journal of Medicine*, observes that "some scientists might ask: Why limit ourselves to naturally occurring genetic variants? Why not use synthetic biology to write new cellular circuits that, for example, cause cells to commit suicide if they start down the road toward cancer?" (40). We could also imagine that some would want to edit in a gene that only exists in nonhuman animals that has some benefit to humans.

A barrier could be placed between "a gene variant that any human has ever had" and "a gene variant that no human has ever had." If one human with a beneficial mutation was found, and that variant was edited in to children, that would be upslope. That is, this barrier is very far below the somatic/germline (and disease/enhancement) barriers.

The acts on the two sides of the barrier would remain dissimilar because the difference between humans and other life forms is nearly universal across cultures and is so strong that many scientists have concluded that humans have been designed by evolution to make these distinctions (41). While structurally strong, this barrier would require values like "following nature" or "following God's will" that would define humans and other life forms distinctly. In sum, this barrier is structurally strong, defendable by values, yet values not prominent in the current debate. Since it would allow the enhancement that excited the eugenicists, it is so near what most people consider to be the bottom of the slope that it would probably not be worth establishing.

The Most Prevalent Variant Barrier. There is a strong barrier that could be built between the somatic/germline and the bottom of the slope. Advocates of the value of justice (or fairness) have written that HGE could be used to "create a level playing field for those whose traits now put their children and descendants at a disadvantage" (30). That is, children who would be disadvantaged due to a genetic trait, be it a disease or intelligence, could be given an "equal opportunity" by raising them to what Buchanan et al. call a "genetic decent minimum" (12). Justice would also require that we not allow genetics to be used to obtain social advantage—"a problematic enhancement is one that confers a social advantage beyond that which an individual possesses by fate or through personal effort, and that does not benefit the rest of society in any way or undermines the implicit goals of a competition" (30). Justice would then be advanced by allowing offspring to be edited so that they become ordinary. The key is that becoming ordinary relieves disease—disease, by definition, is not ordinary—but you also cannot gain social advantage over others by becoming ordinary. For example, the reason an Ivy League degree gives advantage is that it is rare, not ordinary. Justice is one of the few values supported in this debate.

This value could support a barrier at "the most prevalent variant" that will produce an "ordinary" human body at exactly that trait. Diseases are not produced by the most prevalent variant. If they were, they would be considered dysfunctions that are part of the human condition, like aging. Moreover, if the most prevalent variant was dysfunctional for the body, presumably it would have been selected against in evolution.

There is no slipperiness around this barrier because there is only one variant that is the most prevalent—there is no question which modifications are on which side. I show elsewhere that this barrier can be modified for use in a debate far in the future where polygenic selection or modification is possible. I also address the many challenges to this barrier that can be imagined, such as which reference population to use for the "most prevalent" determination and variants that are beneficial in some contexts and not others (5).

Let us locate this barrier on the slope. It is well below the somatic/germline boundary because it is distinguishing between allowable and unallowable germline interventions. It is also agnostic to the disease/enhancement distinction—you could improve a child's health or their intelligence, as long as you make them ordinary and not give them social advantage. This is the ground on the slope that has to be sacrificed when the disease/enhancement and somatic/germline barriers fall.

As a concrete example, pretend that there is one gene that determines height, and taller people have social advantage. Further imagine that the child that would grow from your embryo would be two SDs below average height. The most prevalent variant could make that child average height, which is not going to give them social advantage, but will give them a "genetic descent minimum." This would be above the barrier and allowed. If your embryo already had an ordinary variant, giving them a rare variant producing even more height would be below the barrier and not allowed because that would provide more social advantage than they otherwise would have.

While the barrier has a very strong design, like all barriers it can be damaged by a change in values in the debate, like the somatic/germline barrier was damaged. For example, if we only used the value of respect for autonomy, this barrier would be knocked over because it would be up to the parents if they wanted to give their child genetic advantages over others. With that said, this is one of the few structurally strong barriers that can be identified between the somatic/germline barrier and the bottom of the slope.

Conclusion

For over 60 y, scholars in the West have been debating which acts of HGE we should allow. A number of barriers on the slippery slope have been built, and the most prominent have been the disease/enhancement and the somatic/germline barriers. The disease/enhancement barrier fell prey to our increasing knowledge of gene function. The somatic/germline barrier could have been felled many decades ago as the values in the debate changed, but its extremely strong design of radical dissimilarity of the two sides, and a lack of motivation for knocking it over, led to its continuation into the CRISPR era. Given that nonmaleficence (safety) is the only value currently supporting it, once germline HGE becomes safe, the barrier will immediately fall. The debate is currently without any barriers between the dilapidated somatic/germline barrier and the dystopian bottom.

With the exception of people who want to get to a world of germline enhancement as soon as possible, or those who believe that people should have the reproductive freedom to do so, a barrier is required. I identified a number of possible barriers below the somatic/germline. Some have a weak design and will not hold once our technological ability reaches them. Others have a strong design but are far downslope. All require values that support them. Ideally, the ethical debate that feeds into public policy would be based on the public's values, but that is not currently the case.

Finally, the CRISPR revolution is making all sorts of intervention into the natural world possible, and these interventions all have their surrounding ethical debates. The analysis I have engaged in here could be replicated in at least debates about plants and animals—should there be a limit on what sorts of plants and animals are created? A well thought-out barrier based on the public's values would likely have, for example, genetically modified golden rice upslope of such a barrier and a fully synthesized world below the barrier (42). Such an analysis requires thoughtful consideration of the values underlying these debates and the identification of barriers that best support those values. With genetic tools becoming more and more powerful, we must focus on why we are using the tools—on our values—or risk sliding into "what can be done should be done."

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