

# Gene Editing: New Technology, Old Moral Questions

Brendan P. Foht

The fears and the hopes of genetically engineering the human race have been haunting the modern mind for the better part of a century, although only in the last decade have techniques been developed that might give us the power to modify the genomes of human beings at the embryonic stage. Foremost among these has been the CRISPR-Cas9 system—a set of bacterial enzymes first identified in the late 1980s, and during just the last few years harnessed as a gene-editing tool. What sets CRISPR apart from earlier genetic modification techniques is its accuracy and versatility: the enzymes that cut the targeted DNA are guided by short sequences of RNA that can be custom-designed for any site in the genome. Earlier genetic engineering methods required different enzymes to target different locations in the genome, but by using RNA instead, CRISPR makes that targeting process much easier. (Although there are some differences in what the terms "genetic engineering," "genetic modification," and "gene editing" mean, they are for the most part interchangeable.)

This new gene-editing tool has rapidly become ubiquitous in molecular biology, with many applications beyond gene therapy. For instance, scientists have used CRISPR to remove retroviral sequences from the genomes of pig embryos in the hope of producing pigs with organs that can be transplanted more safely into humans. Because CRISPR is relatively easy to use, some journalists have even speculated that the technique might lead to the democratization of genetic engineering, with "home hobbyists" using it for who-knows-what. This claim seems overblown. While it is true that CRISPR makes the specific task of editing DNA much easier, there are other technically complicated steps and procedures involved in most forms of genetic engineering. To alter genes in a child or adult, human cells need to be cultivated and modified in a lab before being transplanted back into the person's body, all of which represents a significant technical challenge. And modifying the genes of human embryos would mean first conducting in vitro fertilization—a procedure that would be very difficult for an amateur hobbyist and is made no simpler by CRISPR.

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Still, it seems as though CRISPR may be poised to overcome the major technical hurdles to genetically engineering human beings—namely, being able reliably and precisely to modify the DNA sequences of human cells, including embryos. Scientists have already used it to create genetically modified mice, pigs, and non-human primates. There have even been two published studies describing the use of CRISPR by Chinese scientists to modify human embryos (which they subsequently destroyed); it is generally believed that scientists in China have conducted numerous similar experiments without publishing their results. In the published studies, the error rates in the genetic modifications were very high, but other researchers have discovered ways to improve the accuracy of the technique significantly, and so it may soon be precise enough for clinical use.

The scientific and media interest in CRISPR has renewed longstanding debates about the ethics of genetically engineering human beings. The questions we face: Should we design our descendants? And if so, how? What are the proper ethical boundaries around this new power, and what are the proper ends to which we should direct it? What are our obligations to future generations—should we take control over our evolution so that our descendants may transcend human nature, or ought we to consider human nature to be a gift from our ancestors for the present generation to steward faithfully for the good of generations to come?

#### **Foreseeable Limits**

Before assuming that CRISPR will transform genetic therapy and make possible designer babies and other forms of genetic enhancement, it is worth reviewing some of the remaining practical and technical obstacles. Regarding therapy, we should remember that clinical genetics has so far had limited success even in the areas of diagnosis and prediction, and it is not at all clear that the addition of this new technique for modifying DNA will be useful in treatments anytime soon. Likewise for enhancement: the project of designing our descendants to be (for example) tall, smart, athletic, and creative would require us to know the precise genetic basis for these traits so that we could decide which pieces of DNA to change. We are far from having such knowledge today.

Biotechnological optimists who expect that CRISPR will quickly advance point with hope to the great progress over the past several decades in the closely related field of gene sequencing. The U.S. government spent almost \$4 billion and about fifteen years to sequence just a single human genome from 1988 to 2003. Now, private companies can

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sequence a human genome for as little as \$1,000, and the British government has embarked on a \$0.4 billion project over three years to gather 100,000 whole genome sequences. There is more to evaluating these technologies than these raw numbers, of course, but the numbers tell a very important part of the story.

However, while the record of progress in gene sequencing is indeed remarkable, measuring progress in the science of genetics or the art of medicine is not as simple. If anything, the technological progress has far outpaced medical and scientific progress. The field of clinical genetics, which involves diagnosing and predicting disease on the basis of genetic factors, is still riddled with errors that result in bad medical decisions, including, most troublingly, the abortion of children who are mistakenly diagnosed with genetic diseases.

And so, as we discuss how CRISPR might be used in medicine, we should keep in mind that gene therapy will never be more effective than the level set by clinical genetics. If we do not know enough to predict or diagnose disease on the basis of genetics, we will not be able to cure or prevent disease through gene-editing techniques. Clinical genetics will likely improve in coming years as scientists gather ever more data from ever more patients, and we can expect that therapies for specific genetic disorders—especially those associated with a small number of genetic mutations—may be available in the years ahead. But even if we had a robust understanding of the mutations that cause disease, we would still be far from understanding the genetic basis of complex traits such as athleticism or intelligence that parents might seek to design in their offspring.

## Gene-Therapy Ethics: Somatic vs. Germline

The conventional wisdom that has taken shape around genetic technologies holds that we should sharply distinguish between "somatic" gene therapies (which we are supposed to consider largely acceptable) and "germline" gene therapies (which we should oppose). The former category involves genetic changes that are not passed on to children, such as the various gene therapies used for the past two decades to treat disorders of the immune system. By contrast, the latter category involves genetic changes that are passed on through the germ cells (sperm and egg) from parents to children. This can be done in two ways:

(1) Genes in the germ cells of children or adults can be altered, and so any embryos produced using these sperm or egg cells will contain the modified genes in all of their cells. (Women do not produce new egg

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cells after birth, so this kind of germline treatment is more likely to be attempted in men; their sperm-producing stem cells could be modified by gene-editing technologies.)

(2) The genes of an embryo can be modified; its altered genes would end up in cells throughout the developing child's body, including the sexcell-producing cells.

The germline seems at first to represent a convenient "bright line" for ethicists and policymakers. Unlike with blurry categories distinguishing between acceptable therapy and unacceptable enhancement-or more generally, the distinctions between prudent and reckless, safe or dangerous, good or bad-it is easy to see the difference between, on the one hand, therapy in children or adult patients, and on the other, intentional modifications to the germline. One reason germline modifications are often deemed ethically distinct, writes science historian Nathaniel Comfort, is that they "are not used to treat disease in an individual, but to prevent it (or lower the risk) in future individuals." However, this depends, to some extent, on the type of germline modification, on what or who counts as an individual, and on the intentions of those providing the therapy. Modifications of an adult patient's egg- or sperm-producing cells do not treat disease in that patient, but would rather prevent disease in that patient's yet-to-exist children. But modifying the genes of an early embryo would treat, or at least prevent, disease for that individual, the embryo, in addition to preventing the disease in any descendants that embryo may one day have. In this sense, modifying the genes in an early embryo may be *intended* as a somatic therapy (since the embryo is a body, or *soma*) but it has the unavoidable "double effect" of modifying the germline. So ethical analyses that try to distinguish between somatic and germline modifications may not be as clear-cut as they seem, since modifications of the germline may arise as consequences, rather than as intended aspects, of modifications made for the benefit of the embryo.

(The complexity of germline ethics is further illustrated by the debates over another reproductive biotechnology: the mitochondrial replacement techniques recently approved for use in the United Kingdom. These techniques, intended to prevent the transmission of certain diseases, involve transferring DNA between two egg cells to create an embryo that will have nuclear DNA from one woman and mitochondrial DNA from another. Since the children created via this technique would have DNA from two women, some critics have argued that it "would constitute germline modification." However, because mitochondrial DNA is only inherited maternally, the U.S. National Academy of Medicine, in its February 2016 report on the social

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and ethical implications of mitochondrial replacement techniques, proposed that doctors implant and bring to term only male embryos created through this procedure—meaning that female embryos would all be destroyed—so that the modifications will not be passed on through the generations.)

## The Problem of Consent

A concern sometimes raised with germline modification is that of consent. For instance, Paul Knoepfler, in his recent book *GMO Sapiens*, describes parents who choose to genetically modify a child "(particularly for a non-medical reason) as having forced that decision on the future child without [the child's] consent."

But it is not only future generations who are unable to consent to medical procedures; children in general lack the legal, moral, and practical ability to provide freely given informed consent. Newborn babies, for example, are not able to consent to the various medical treatments they receive in hospitals—including, sometimes, experimental treatments for rare or difficult-to-treat conditions. Experimental therapies may be justified for children when such therapies are medically necessary for them, even though the children cannot consent to the risks.

Properly understood, then, the question is not about consent *per se* but about whether and how the well-being of future generations ought to enter into medical decisions. If a treatment, such as genetic modification, seems necessary for a patient here and now, should we withhold that treatment because it might affect the patient's as-yet-unconceived offspring? An embryo, having been brought into existence, is a human organism with medical needs—an embryo can be cared for well or badly, and will live or die, or grow to be healthy or sick, in part on the basis of how it is cared for in its earliest stages. A single-celled embryo carrying two copies of a mutation that causes cystic fibrosis arguably does not yet have the disease (it will not exhibit any of the disease's symptoms at this stage), but that organism will over time develop the disease. Editing those mutations is then a form of preventative medicine—not, principally, for future generations, but for the embryo, and for the child and adult that the embryo will grow up to be.

## The Germline in Eugenics

When new biotechnologies such as cloning or embryonic stem cells emerge, they sometimes pit a pro-research scientific community against members of the broader public who have moral concerns. Biologists often seem to follow J. Robert Oppenheimer's famous dictum that "when

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you see something that is technically sweet, you go ahead and do it." On the other hand, some biologists also seem to take seriously another of Oppenheimer's well-known remarks: that scientists "have known sin; and this is a knowledge which they cannot lose." For biologists that sin was the participation in the eugenics movement of the early twentieth century, a set of ideas and policies notoriously aimed at perfecting the human race (or arresting its decline) by controlling human heredity.

The human germline—or, as it was then known, the "protoplasm" or "germ plasm"—was seen by eugenicists as "the most precious thing in the world," in the words of a 1926 "Eugenics Catechism." The aim of eugenics was to preserve this precious protoplasm from the deterioration it faced as modern civilization allowed more and more people to survive and reproduce who might otherwise have been eliminated through the process of natural selection.

Today, those who are familiar with the legacy of eugenics in the United States tend to find most repugnant the practice of compulsory sterilization of the so-called "feeble-minded" and others judged genetically unfit. Such eugenic sterilization was a perversion of the aims of medicine—surgically manipulating the bodies of patients not to preserve or restore *their* health but to improve or preserve the quality of society's "germ plasm"—the mutilation of patients as a public health measure.

Following the discrediting of eugenics, human genetics turned down a more medical path, one aimed at helping actual patients instead of protecting the germ plasm from deterioration. Today, some critics fear that advocates of human enhancement might use the new gene-editing techniques to manipulate the germline—a kind of backsliding to the use of genetics not for the medical benefit of individual patients, but for the sake of that non-patient, the human race. However, as we shall see, this justified fear of the eugenic implications of modifying the germline can itself lead to the subordination of the well-being of actual patients who might themselves stand in need of genetic therapies that could affect future generations.

#### Where Germline Talk Leads

Within the scientific community, views about germline modification are mixed. In an opinion piece published in the journal *Nature* in March 2015, four authors from the fields of biotech and regenerative medicine, together with an ethicist, argued that human embryos (at least those that will be allowed to grow into children) should not have their genes modified because such actions "could have unpredictable effects on future

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generations." However, the next month a letter to the journal *Science*, written by a group of scientists, legal scholars, and bioethicists, expressed more optimism, describing a "prudent path forward for genomic engineering." For the time being, the authors "strongly discourage" clinical applications of germline modification, but they encourage continuing research "relevant to its potential applications for germline gene therapy."

This latter view, which might be called cautious optimism, was also the position taken by the organizers of an international summit on gene editing held in Washington, D.C. in December 2015. The summit's twelve conveners—including such prominent scientists as David Baltimore and Paul Berg, who had participated in the debates over recombinant DNA in the 1970s, and Jennifer Doudna, who is widely credited with codiscovering CRISPR—issued a statement recommending that if "early human embryos or germline cells undergo gene editing, the modified cells should not be used to establish a pregnancy."

To this way of thinking, one condition of experimenting on human embryos is that those experiments must have no chance of therapeutic value for the embryos—a disturbing inversion of the care that we ought to provide for the most vulnerable. By recommending to destroy embryos so that their edited genes will not pollute the germline, these influential scientists and ethicists seem to be falling back into the errors of the eugenicists—valuing the abstraction of the "germline" above the lives and medical interests of actual human beings.

The position that permits genetic modification of embryos only if they will be destroyed should not be seen as a compromise between a total ban on embryo experimentation and complete permission for the modification of the germline—rather, in mandating the destruction of certain types of human beings, it should be seen as one of the worst ethical outcomes.

# Imperfection and Gratitude

Some biologists are suspicious of genetic engineering out of a deference to the wisdom of the evolutionary process that has generated so many remarkably well-designed organisms. The axiom that "evolution is cleverer than you are," attributed to biologist Leslie Orgel, is widely accepted by biologists who recognize that our evolutionary heritage has left us, on the whole, well-adapted to our environment.

Not everyone shares this view. Allen Buchanan, an advocate of at least some forms of human enhancement, has argued that Darwin considered evolution not to be a "master engineer" but rather to be a "morally blind,

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fickle, tightly shackled tinkerer." In support of this view, Buchanan is fond of citing a famous passage from one of Darwin's letters in which he wrote, "What a book a Devil's chaplain might write on the clumsy, wasteful, blundering low & horridly cruel works of nature!" However, read in its context, this bit of purple prose seems to have been meant in jest. And if we consider the book Darwin did in fact write, *On the Origin of Species*, we find a very different appraisal of the evolutionary process:

Thus, from the war of nature, from famine and death, the most exalted object which we are capable of conceiving, namely, the production of the higher animals, directly follows. There is grandeur in this view of life, with its several powers, having been originally breathed by the Creator into a few forms or into one; and that, whilst this planet has gone cycling on according to the fixed law of gravity, from so simple a beginning endless forms most beautiful and most wonderful have been, and are being, evolved.

A literary interpretation of Darwin's writings will not settle the question of whether evolution is more like a master engineer or a clumsy tinkerer, nor whether we would be better off deferring to the wisdom of nature or embarking on a technological program of changing it. Darwin may have been wrong to think of the production of higher animals as the most exalted object we are capable of *conceiving*, but the human form, and the forms of the rest of the living kingdom are the most wonderful and beautiful and well-formed objects that anyone will ever behold.

This is not to say that human nature, or the nature of any living creature, is perfect, but to express a sense of gratitude and wonder at what is good about us before expressing dissatisfaction with our faults. Buchanan identifies a few areas where we are less than perfectly "designed"-for instance, some forty million years ago, a mutation caused our ancestors to lose the ability to produce their own vitamin C. We need not quarrel with the assertion that it would be better for us to have the natural ability to synthesize vitamin C, that the evolutionary accident that caused us to lose this ability represents an imperfection in our nature. But what follows from admitting that it is an "imperfection" at all? Surely it would be more reasonable to leave our evolved nature as it is and to drink some orange juice than to embark on a genetic engineering project to give our descendants freedom from their dependence on citrus. Just as in politics it is easy to *imagine* better regimes but very difficult actually to design and build new ones, in biology it is easier to recognize what we might call a deficiency than it is to correct one. In biology and medicine, as in politics,

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a sense of gratitude for what works in deeply complex, evolved systems should take precedence over a sense of dissatisfaction with what does not.

# A Pro-Life Case for Therapeutic Gene Editing

The options available to parents who know that their children face a risk of inheriting a genetic disease are to refrain from having children (either through abstinence, contraception, or sterilization); to use IVF and preimplantation genetic diagnosis (PGD)—a technique that involves extracting cells from early embryos in order to determine whether the embryos carry certain disease-causing genes, and then selectively implanting only the embryos not affected by those genes; to use donated sperm, eggs, or embryos; to adopt; or to have a child naturally and (if the child is affected by the disease) use whatever postnatal treatments are available.

As gene-editing technology improves, it will not only become easier to edit the genomes of embryos, but it will also become easier to cure or treat diseases in children or adult patients—and in many cases, such somatic gene therapies will be preferable to editing the genes of embryos. However, some genetic diseases manifest in early stages of development; most forms of Tay-Sachs disease, for instance, begin to manifest early in pregnancy and are generally fatal for the child before it reaches the age of five. In such cases, correcting mutations after a baby is born may not be an effective way to reverse developmental problems caused by the mutations. Editing the genes of embryos would presumably be more effective, though also more dangerous, than postnatal gene-editing, since it would affect a much greater proportion of the body's cells and will do so from an earlier stage of development.

Some critics of human germline modification, such as the authors of the *Nature* opinion piece from March 2015, think that "Established methods, such as standard prenatal genetic diagnostics or *in vitro* fertilization (IVF) with the genetic profiling of embryos before implantation, are much better options for parents who both carry the same mutation for a disease." However, preferring PGD over genetic therapy represents a troubling attitude toward people with disease and disability. In selecting embryos to destroy (or fetuses to abort), doctors and parents are making a judgment that the life of someone affected by a disease or disability is not worth living—implying that those individuals affected by the disease would have been better off if they had never been born.

To put it another way, the judgment implicit in using gene editing to modify a disease-causing gene is that it is better to live without that

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disease than to live with it; the judgment implicit in using prenatal abortion is that it is better to die than to live with the disease. When both are options, preferring selective destruction over gene editing amounts to a preference for killing over curing.

In debating the future of genetics and medicine, we should remember that the current practice of prenatal screening and abortion is not the beginning of a slippery slope but is rather already the bottom of that slope. It is the medically sanctioned use of killing as a public health measure. Morally speaking, editing the genes of embryos rather than destroying them would be a step in the right direction.

However, given how the assisted reproduction industry operates in the United States, it seems unlikely that gene editing will replace PGD anytime soon as a way to prevent genetic disease. American IVF clinics regularly produce many more embryos than they will attempt to implant, so as to improve the efficiency of the procedure and to maximize the chances of achieving a pregnancy. This means that, in American IVF clinics, many more embryos are destroyed for the sake of convenience and efficiency than are destroyed for the sake of avoiding genetic disease. Likewise in the case of abortion, while the majority of babies diagnosed with Down syndrome are aborted, the majority of abortions are not done for such eugenic reasons. A culture that so often treats embryonic and fetal life as discardable is unlikely to bother with an inconvenient and difficult therapeutic approach instead.

There are some cases where PGD is not an effective option—for example, where both parents carry two copies of recessive disease-causing genes, or where at least one parent carries two copies of a dominant diseasecausing gene. These will always be very rare cases, however, representing a small minority of the population. Furthermore, these kinds of cases would by definition only involve diseases that are later-onset and less serious than the most lethal genetic diseases, since they would involve prospective parents who are not just carriers but are themselves patients affected by the disease who have nonetheless survived to adulthood. These kinds of cases might be good candidates for postnatal gene therapy instead of editing the genes of embryos.

## Editing Genes to Make Better Children

While PGD and selective abortion can be used for negative eugenic purposes—that is, to eliminate undesired embryos or fetuses—it is far harder to use them for positive eugenic purposes, such as designing or choosing

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complex traits in one's offspring. Other than the obvious example of the sex of the child, very few non-disease traits can be selected using these techniques. PGD will never be an effective way for parents to design a child who will be genetically disposed to be tall, intelligent, good-looking, or athletic, since these are all traits that involve dozens, or hundreds of genes, to say nothing of environmental factors.

But gene-editing techniques such as CRISPR may offer parents the ability to modify large numbers of genes in their embryos to give their children a better chance of being tall, intelligent, good-looking, or athletic. However, designing these kinds of traits would require not just an effective gene-editing technology but also precise and extensive knowledge of the genetic basis for these traits. Traits such as intelligence involve very large numbers of genes that each make a very small contribution. Picking the genes to modify in an embryo in order to create a child with, say, a high IQ, would require comprehensive knowledge of the actual effects of different genes. Having a vague awareness that IQ is heritable might motivate the selection of a high-IQ sperm or egg donor (or husband or wife, for that matter), but it is not enough when faced with the decision of which exact nucleotides to change in a given genome. A particular variant may be associated with slightly higher IQ on average in the population, but without understanding how that variant interacts with other genes and environmental factors to influence intelligence, doctors will not know whether introducing it to the genome of a particular embryo will be helpful, harmful, or simply ineffective.

To carry the editing metaphor further, we might compare a technology such as CRISPR to a keyboard. To edit a novel, you need a reliable keyboard, so that when you want to make some correction you don't end up introducing new typos or errors. But a good keyboard will not help an editor who does not understand the basic principles of grammar, spelling, syntax, and so forth. Right now, scientists understand some of the basic syntax of the genetic code-although, as in English, there are many exceptions to any of the known rules. This means that scientists can identify some obvious genetic errors or mutations that cause disease. But to go beyond simple copy-editing to improving the clarity or eloquence of a text, an editor needs to know something of how to convey meaning with words, sentences, paragraphs. Here, scientists are far from having that kind of mastery of the genetic language. Indeed, the metaphor of code and language breaks down quite quickly beyond the rules that govern the translation of a sequence of DNA to a sequence of amino acids. (Indeed, the use of the term "editing" shows how much we have come

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to understand DNA as an information-bearing code, whereas the older term "genetic engineering" puts more of the emphasis on the mechanistic aspects of molecular biology; both are metaphors, however, and neither is quite right.)

While there are currently strong practical limits on genetic modification of complex traits, it is still worth questioning the aims of one day doing so. Larry Arnhart has argued in these pages that genetic engineering will always be constrained in the goals to which it will be directed, since parents have a natural desire for what is best for their children, which will guide their decisions about genetically modifying them. Arnhart is right to think that scenarios such as the one depicted in Brave New World, where the state takes over reproduction and designs children to be genetically suited to particular social roles, are highly unlikely, particularly in a liberal democratic society. Advocates of reproductive technology in the United States are not arguing for greater social stability or for taking control over reproduction away from parents and giving it to experts; rather, they hope to give parents the opportunity to overcome chance and to exercise free choice not only over when and how they have children but over what their children will be like. Nevertheless, even though parents will have what they take to be their children's best interests at heart when making choices about genetic traits, this is obviously no guarantee that they will act wisely.

Advocates of enhancement often point to how genetic engineering would be, in principle, no different from the kinds of control that parents already exercise over their children: sending them to private schools, forcing them to take piano lessons, and generally putting pressure on them to succeed. Parents certainly have a right and a responsibility to do what they can to get their children to grow up to be productive, law-abiding, virtuous citizens, and we should not, in arguing against the genetic control of children by parents, end up arguing that children should have anything like absolute freedom from parental influence and guidance. But parents are bound to make mistakes. One hopes that parents will not have made so many mistakes that their children will be unable to grow into mature adults able to assert their own identities and their own interests. On top of the natural imperfections of parental wisdom, the world has seen no shortage of misguided educational and parenting fads-radicals of all stripes have had all kinds of ideas about the best ways to raise children, but thankfully, these ideas have never had much enduring success or done much lasting damage. But the genetic engineering of our children could be different. As Yuval Levin has noted in these pages:

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Direct interventions in children's bodies and minds, and particularly genetic interventions or selections that may extend to further generations beyond, would make permanent the preferences of the present, and would subject future generations to our whims. It has been very good for us that the raw material of humanity remains raw in every generation.

Imposing our expectations and wishes on children can be harmful in normal cases, but at least children can assert their individuality and set off in their own directions. A boy who is more interested in art than baseball can tell his father that he would rather paint than try out for the team. But a boy who has been genetically designed to have more muscular arms to better hit home runs can say nothing to push back against the way his parents' expectations are inscribed in his body. Of course, he can still choose not to play baseball, but he will then not only be disappointing his parents' expectations but also, in a sense, frustrating the design of his own nature, which has been deliberately shaped by his parents to be suited to a particular way of life of their choosing, not his. Far from licensing more extensive control over the genetic traits of our children, the fact that parents have been susceptible to imposing their expectations of how their children should be is just what should make us suspicious of projects for human enhancement in the future.

Few subjects raise the same levels of fear and hope as genetic engineering, but a prudent approach, drawing on lessons from history, will help to mitigate both the alarmism and the utopianism that characterize debates over new genetic technologies. The legacy of the eugenics movement should teach us of the dangers of elevating abstractions like the "germline" above the needs and medical interests of actual patients. This means that we should remain open to allowing gene therapies to cure or prevent genetic disease, even when doing so may affect future generations. At the same time, we must recognize the dangers of increasing our power over future generations. These dangers lurk in the ways our society sometimes treats children as objects to be manipulated rather than as new human beings who call for unconditional love, acceptance, and nurturing from their parents. Looking to our past, we should cultivate a sense of gratitude and reverence for what our ancestors have bequeathed to us-our evolved human nature, which brings forth bodies and minds that are awe-inspiring, frail, and beautiful beyond anything in this world: It is a gift that we should steward responsibly for our children and for generations to come.

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