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COMMENTARY

Nature beyond control: how expectations should inform decisions about human germline engineering

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Abstract
In the ongoing discussion about the risks of reproductive human germline modification, scant attention has been paid to whether it could be reconciled with theories of psychological well-being. Even if safety and feasibility challenges could be overcome and germline engineering technology could be implemented in ways that avoid exacerbating social inequality, we would still have to question whether germline modification would promote circumstances that lead to better psychological experiences for parents, society, and the genetically edited person. This paper posits that germline engineering would produce expectations of being able to control the manifestation of an individual's characteristics, which will inevitably be upset by our limited understanding of how genes interact with each other and with the environment. Drawing on self-discrepancy and relative deprivation theories, it is suggested that both editing and being edited could lead to unmet expectations and thus negative emotional states that would offset benefits of successful intended genetic changes.

Keywords Germline engineering · Expectations · Control · CRISPR · Ethics · Self-discrepancy theory · Relative deprivation theory

Introduction

Ethical concerns about human genetic engineering (HGE) are being reinvigorated by the refinement of CRISPR-Cas9-based gene editing. Most prominent are questions about how the practice would affect safety and physical health, followed equally by whether just access could be ensured, exacerbation of socioeconomic stratification prevented, and rights to self-determination protected. Those who advocate for HGE believe it can improve the human experience by modifying the genetic basis for how we develop physically, but seldom consider whether attempts to genetically modify our physical development could lead to states that promote psychological well-being. This paper posits that germline engineering (creating heritable changes in embryos) carries expectations of being able to control the manifestation of an individual's characteristics, which will inevitably be upset by our limited understanding of how genes interact with each other and with the environment and by the role environment plays in human identity formation. Drawing on self-discrepancy and relative deprivation theories, it is suggested that germline editing could lead to unmet expectations and thus negative psychological states for parents and the child that could offset the benefits of successful intended genetic changes. At minimum, the potential for unmet expectations of HGE should guide the development of policy around allowable edits and how providers discuss such edits with potential patients/clients. At maximum, the potential for harm from unmet expectations combined with the availability of other options, such as in vitro fertilization combined with preimplantation genetic testing (IVF + PGT) or adoption, to avoid deleterious physical states means that germline engineering should not be pursued.

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Jiankui experiment

Using genetic engineering to either treat diseases in living humans or modify the genomes of embryos is no longer just a thought experiment thanks to the discovery of an

evolutionary immune response in bacteria termed clustered regularly interspaced short palindromic repeats (CRISPR). This naturally occurring system, which allows bacteria to incorporate genetic "snapshots" of potentially harmful viruses into their own DNA for future reference, can be coopted and combined with RNA-guided enzymes (Cas9) to target, cut, and replace specific sequences in a genome [1]. In comparison, traditional models of gene modification, including zinc fingers and TALENs, which rely on protein engineering are cumbersome, expensive, and time-consuming. CRISPR-Cas9's promises of efficiency and simplicity have led to unprecedented investment in related research and a massive patent war that will determine who controls the technology [2].

On November 25, 2018, He Jiankui, a scientist at the Southern University of Science and Technology in Shenzhen, China, announced that he had created the first babies from germline-edited human embryos using the CRISPR-Cas9 gene editing tool. The birth of twin girls, to whom he referred as "Lulu" and "Nana," was celebrated as a success by He and his research team, though the experiment was overwhelmingly condemned by his Chinese colleagues and the international scientific community. The procedure, which was reportedly carried out for protective purposes, involved altering CCR5, the gene responsible for infection of the AIDs-causing virus. According to He, the girls' father was HIV-positive, and his goal was to give the girls the genes for a mutation thought to protect some northern Europeans from HIV infection. However, the edits did not successfully create the intended mutation in either embryo. One twin had a normal CCR5 allele on one copy of the relevant chromosome and the intended edited version on the other copy, significantly reducing her viral resistance, and the other had two edited copies, but neither copy had the intended edit known to confer resistance [3]. He knew this prior to implantation, yet implanted the embryos anyway. He did not abide by his scientific duty to publish results, and the 23-page consent form given to the twins' parents did not adequately describe the risks [4]. This first experiment is fraught with deceit and safety concerns and will likely lead to unmet expectations for the parents and the genetically edited people. Even if the next researcher who intends to engineer the human germline avoids all of He's mistakes, the results could lead to unmet expectations with negative psychological outcomes.

Imperfect editing system

In the wake of the He Jiankui experiment, it is time for the ethical arguments against germline engineering to gain new traction. The strongest and most immediate arguments as to why germline engineering should not be pursued are grounded in concerns of safety and efficacy. If experiments on embryos do not go as planned—and there is significant reason to think plans might continue to go awry even in more rigorous experiments than the one performed by He—the resulting people might experience serious physical or mental harm. These harmful effects would be encoded in heritable DNA and thus transmissible to offspring. The potential harm that would be experienced by the edited person should be enough to reconsider when, if ever, we are ready to pursue germline engineering. This paper argues that such unexpected outcomes might cause additional psychological harm—namely, anxiety, stress, frustration, and depression associated with unmet expectations—which has yet to be well considered in context of germline engineering. It is also here suggested that psychological harm might occur even if the intended genetic changes are successfully carried out. Thus, this potential psychological harm lends additional weight to existing safety concerns (i.e., harm caused by genetic edits not working as planned) and adds a new argument to ethical concerns grounded in human flourishing (harms that would occur even if genetic edits work as planned).

The limitations of genetic knowledge explain in part why expectations of germline engineering might go unmet. We are uncertain as to how CRISPR-Cas9 would work in humans, with the one existing case study demonstrating incomplete editing of the CCR5 gene in both babies and being too recent to know long-term effects. We have much to learn regarding interactions between genes, and between genes and the environment. CRISPR-Cas9 editing relies on RNA-guided DNA endonuclease enzymes that target the specific gene sequence, which contains the mutation responsible for the physical condition that is intended for elimination or activation [1]. While this system is quite reliable in its ability to successfully cut at the desired location in the genome, it has been discovered making cuts at unintended locations that might play important roles in genetic expression and has been discovered inserting or deleting undesired bases at the intended location (called "indels") [5, 6]. Even in the trial conducted by the lab at Oregon Health Sciences University, which targeted a simple four base-pair gene for heart disease and demonstrated the greatest accuracy to date, the team reported over 25% indels in examined embryos [6].

The consequences of unintended genetic changes could result in physical problems the same or worse as those that were targeted for elimination. To complicate matters, the only way to determine whether the embryo is free from unintended genetic edits is to examine the DNA in each cell, which requires breaking apart the embryo thus preventing implantation. At some point after thoroughly examining a significant number of embryos for mistakes, which will result in their destruction, a clinician-researcher who wishes to implant an embryo will have to do so without a complete examination. What level of accuracy in previous trials and what condition-causing mutation would justify implanting an incompletely examined embryo? Even if the editing environment can be

controlled well enough to suggest the implanted embryo likely carries no unintended edits, its development in utero will have been untested, which could lead to further changes. For example, will systems designed to turn CRISPR-Cas9 off at the right time still work in an implanted embryo [7]?

Even if we can assume that CRISPR-Cas9 has only made intended edits, it is possible that the targeted gene is responsible for more than expected. Genome-wide association studies (GWAS) suggest that mutations in specific genes lead to specific conditions, and when that gene presents as the "normal" type, the condition will not manifest. But these studies do not suggest how changing the mutation for gene A might affect genomes that have never known a normal type for gene A. Accurately eliminating the mutated gene A and restoring it to normal type might cause an unintended consequence in conjunction with genes B, C, or D. One example of this is the discovery of an alternative pathway to a disease leading to inability to metabolize vitamin B_{12}. It was originally thought this disease only manifested when both parents carried mutant copies of the MMACHC gene. Recently, it was found that in some affected patients, one mutant gene combined with a normal type plus an adjacent "silencer" gene can also cause the disease [8]. Back to our hypothetical, if we edit genes to "normal type" without knowledge of adjacent silencers, the disease might still manifest or cause something else unexpected.

There are several pathways to unexpected outcomes that might lead to physically deleterious states. Unintended edits could cause mutations leading to deleterious conditions or to negation of intended edits (i.e., condition targeted for elimination still manifests). A successful intended edit could have effects on other parts of the genome that might not be well enough understood, leading to unintended conditions or ineffectiveness of the intended edit. An intended edit might be successful, but other parts of the genome or the environment might interact in unexpected ways with the changed sequence, which could cause other conditions, or negate or exacerbate the targeted condition. Finally, even if every aspect of the genetic editing goes exactly as planned, the individual could develop an unrelated but phenotypically similar condition. Each of these possibilities would lead to unmet expectations—i.e., "I edited my unborn child to be cancer-free but she developed cancer anyway"—which would compound the negative physical experience of the manifested condition with negative psychological consequences.

Unmet expectations

Many neuroscientists view human brains as "prediction machines," constantly working toward "prediction-error minimization" [9]. Two theoretical perspectives in the sociology and social psychology literature—namely, self-discrepancy theory and relative attribution—hypothesize the detrimental psychological effects of unsuccessful prediction-error minimization manifested through unmet expectations.

Self-discrepancy theory asserts that unmet expectations are the result of discrepancies or gaps between one's "actual" self-state and one's "ideal" self-state or "ought" self-state [10]. An actual self-state is one's "self-concept," or the representation of attributes that someone believes he or she actually has [10]. The ideal self-state—the individual's beliefs about his or her own or a significant other's hopes, wishes, or aspirations for the individual—and the ought self-state—the individual's beliefs about his or her own or a significant other's beliefs about the individual's duties—are "self-guides" [10]. The pursuit of germline engineering implies at least one aspect of an ideal or ought self-state for the edited person—that of having the physical state associated with the intended genetic edit. The researcher would not attempt, and the parents would not agree to, the study intervention if they did not believe the embryo would be better off with a different genome. But, our limited knowledge of how genes interact with each other and with the environment in addition to the potential shortcomings of the CRISPR-Cas9 system will likely create gaps between actual and ideal/ought self-states for edited people. A person edited to be free of BRCA cancer might develop a different cancer, or a person edited to be more intelligent might not manifest with the kind of intelligence that the parents value.

These gaps create significant negative psychological consequences. Dejection-related emotions, such as disappointment and dissatisfaction, are associated with the discrepancy between one's actual self-state and one's ideal self-state [10]. The discrepancy between one's actual self-state and one's ought self-state is associated with agitation-related emotions like fear, threat, and restlessness [10]. These emotional responses are modulated by magnitude of self-state discrepancy [10]. Germline engineering implies a dichotomous option—receiving the intervention suggests you will be free from the target disease or will carry the beneficial trait. Opting out means you will not. Thus, pursuing the genetic edit only to end up with the disease (or something similar) or without the beneficial trait ensures a severe self-state discrepancy causing psychological distress for the edited person and parents.

Similarly, relative deprivation (RD) asserts that individuals experience psychological distress when not rewarded with an experience to which they feel entitled [11]. According to RD, the source of one's deprivation is relative to the individual's own past, other people, ideals, or social categories. In the context of human germline editing, a parent's notion of an ideal attribute for their future child is reinforced by the researcher who offers genetic edits to achieve that attribute. Parents then feel entitled to a child, if not a permanent lineage, with that attribute if they pursue genetic modification of their embryo. If for the reasons described earlier, the attribute does not manifest as expected, the parents might be deprived of the child for which they hoped and to which they felt entitled. The

edited person would be similarly deprived of a life with the attribute around which their identity might be inextricably formed. Each would suffer psychological distress resulting from deprivation manufactured by the expectation of being entitled to the promised attribute.

Relational and self-impact

To further examine the psychological impact of unexpected gene editing outcomes, we can look to several existing scenarios of unexpected outcomes involving relationships between parents and child, a patient and their physician, and the individual alone. Each of these cases bears relevant similarity to the potential psychological impact that would be experienced by parents and their germline-engineered offspring when our limited understanding of how genes interact with each other and with the environment leads to unfulfilled promises of superior physical states.

Parent-child relationship

Most, if not all, parents-to-be imagine the lives of their future children in terms of their own abilities and values. Often, the abilities, interests, aptitudes, capacities, or fantasies of parents are imposed on their children, and when the children do not share them, parents can be disappointed and/or their children might perceive that their parents are disappointed, which can lead to significant relationship strain [12, 13]. Such disappointment from unmet expectations can be lessened by parents' understanding that children are individuals, separate from themselves, and subject to the genetic lottery and environmental influences beyond their control.

Research shows that the time, attention, and money that today's parents spend on their children are unprecedented in American history [14]. The term "intensive parenting" was coined to describe this "child-centered, expert-guided, emotionally absorbing, labor intensive and financially expensive" phenomenon [14]. One way intensive parenting can become problematic is when parents overcommit their young children to their own notions of valuable activity—i.e., playing instruments or sports, or requiring success in math despite the child's disinterest, discomfort, or limited ability. This parental behavior might in part be motivated by a desire to improve the child's future opportunities (a "tough love" approach) and is also likely the product of the parent's inability to adjust their expectations. Everyone in the relationship can be negatively affected—parental hovering is correlated with high levels of stress and anxiety and found to impede the child's development of social skills, emotional maturity, and executive functioning [14]. Intensive parenting often bears concomitantly specific expectations for the success and well-being of the child, which explains the allure of germline engineering.

Knowing how difficult it is for many parents to adjust their expectations of children who, on some level, parents know are subject to influences beyond their control, it is easy to imagine the challenge being magnified in the case of a child that was germline edited. Inherent in the concept of germline editing is the assertion of control over the physical manifestation of one's child. Even if the motivation is strictly to improve the child's chances for success, or removing barriers often associated with certain conditions, the genetic edits would carry expectations deeper than any of a nonedited child. These expectations are solidified by the significant financial and logistical investments that would be involved in germline editing, including IVF, application of editing technology, screening for successful edits, implantation, and associated costs. A child who was edited to be free from condition X but develops condition X anyway, or a similar condition, is a failure. The relationship is strained between a parent who envisions a child prodigy or burgeoning basketball star and the child who rejects or cannot achieve these visions. If the information became public, peers and other role models would also expect the edited child to behave and perform in accordance with the goals of the intended edits.

A series of studies evaluated parents' prenatal expectations versus their postnatal experiences, each suggesting that expectations play a critical role in adjustment to parental life and psychological well-being [15–17]. Additional literature suggests that few parents prepare for the possibility of their child being born with a disability, and that coping with these differences can cause strain and disappointment leading to crisis [12, 18]. "Gender disappointment"—hoping for one gender and getting another—is a prevalent phenomenon causing guilt and desperation, which has led to the rise of sex-selection technologies [19]. Children with divergent interests, disability, and of any gender should be cognizable possibilities to any parent. One can imagine the psychological distress of a parent who discovers that their child, who was edited to be disability-free, has a disability, or selected for a particular sex does not identify with that sex, or designed to be a math prodigy has trouble with basic equations. One can also imagine the impact of this dissatisfaction on the relationship with the child.

Although uncommon, perhaps the most relevant existing cases to examine are parents who underwent IVF + PGT and had children that were either affected by the condition intended to be screened out, or a similar condition. One study indicated parental regret when IVF + PGT (aneuploidy) did not lead to any implantable euploidy embryos [20], and another described the significant anxiety of two women who learned that their embryos were affected by the diseases that screening was intended to prevent [21]. There is at least one legal case of parents suing a clinic because their child was born with a disease that IVF + PGT was intended to screen out [22]. These cases suggest psychological distress occurs when reproductive medicine offers and then fails to provide

the means for parents to have children without a specific genetic condition. Further studies examining the longer-term psychological impact of unmet expectations in IVF + PGT on parents and resulting children would serve as additional support for the present hypothesis.

Patient-physician relationship

In terms of healthcare, appropriately calibrated expectations are likely important for satisfaction with outcomes. Practically all patients have some expectations for their healthcare interactions. Studies show that a significant source of patient dissatisfaction results from unmet expectations, which can be alleviated when physicians solicit their patients' expectations and work to calibrate them in context of the diagnosis and prognosis [23, 24]. However, it is also suggested that the success of these conversations might hinge on the simplicity of the disorders that are the subject of the interaction [23]. Existing studies of advanced cancer patients demonstrate great difficulty in managing their expectations of chemotherapy effectiveness [25]. It is understandable that a patient's expectations for how easily and successfully the flu can be treated could be better managed by a tactful physician than expectations for the treatment of cancer, the outcomes of which are more serious and less certain. This is also explained in part by the difficulty that patients and most of the general public have in understanding probability [26]. The outcomes of HGE, either gene therapy or germline, are inherently uncertain while at the same time motivated by a promise of control. This paradox sets any clinician-researcher up for failure when attempting to calibrate a patient's expectations for the outcomes of gene editing. A sensible patient or parent-to-be could explicitly acknowledge the risks that gene editing or germline editing might be ineffective or cause worse problems, but their trust in scientific and medical institutions and the power of the notion that genes control diseases could easily preserve unrealistic expectations and lead to psychological harm in the form of frustration, anxiety, and depression.

In the case of the individual who has been genetically edited, either by consenting to gene therapy or being the product of germline editing, there exists the expectation or at least hope that they will be free from the complications associated with the targeted genetic mutation. The edits would not have been pursued but for the belief that they would create a better state of existence. For the gene therapy subject, this endeavor is probably akin to a medical research trial, for which there is a theory that a new treatment method might be superior to existing standards of care. To give informed consent, the patient must be made aware that there is inadequate data to confirm whether the new treatment will be superior and the patient must decide this is a risk worth taking. Under these circumstances, a gene therapy trial might justifiably be used for a serious disease, which does not have a reliably effective existing treatment. There might be some circumstances under which a patient with a terrible prognosis could reasonably conclude that even an untested gene therapy trial would be superior to existing treatments with low demonstrated effectiveness. Empowering the patient to make an informed decision under these circumstances will be a challenge. This patient would pursue a gene therapy trial with the hope that it would lead to a better state than life with the target condition's complications, but the expectation of success could hopefully be tempered by a clinician-researcher who is an effective communicator.

Self-understanding

In contrast, an individual who was germline edited as an embryo to be free of mutations that lead to condition X never had the opportunity to consent to the modification, including weighing it against alternatives. Instead of pursuing IVF + PGT, which reliably screens embryos for the targeted condition to ensure the implantation of an unaffected embryo, and instead of pursuing a gamete donor or adoption, the germline-engineered individual was brought into the world with the expectation of being free from condition X. Their identity is bound by the expectation of not having the complications of condition X. In light of genetic complexity, these or similar complications might still manifest. Beyond the strain on the relationship with their parents who designed them to be without condition X, how will they integrate this state of existence into their self-understanding? There are many examples of people who must reconcile new knowledge or circumstances with their identity, who often experience resulting shock, anger, anxiety, and depression: individuals who have defined themselves by their careers but are forced to retire, those who discover they are adopted after believing otherwise. In the case of the unsuccessfully edited person, they must face the harm of the disease itself and manage the implicit stigma of being a failure.

Drawing a line

It can be argued that expectations are inherent in any form of medical intervention and for any future child. This argument suggests that the possibility of failure or other unexpected outcome should not prevent the pursuit of potential cures to genetic disease, either through gene therapy or germline editing. As described throughout this paper, the specific pursuit of genetic-based cures bears a different expectation of control than do medical interventions or existing forms of child bearing and child rearing. Targeting genes as the cure for disease implies that we should be able to control the complexity of interaction between genes and the interaction between genes and the environment. If it is possible to target and

"correct" some simple genes with a direct genotype to phenotype correlation, there would be nothing to prevent the belief that more effort could lead to the control of more complex genes. But for every single condition that has some genetic basis, environment will mediate its effects. The danger is thus overasserting the power of genetics to predict the physical experience of an individual. This risk is reduced for living individuals with the capacity to consent to experimental treatment, such as gene therapy. In some cases, they will already be experiencing the effects of the targeted condition and might be able to grapple with risks and benefits with an appropriately framed discussion. Under these circumstances, the psychological effects of unmet expectations from gene therapy that fails for any of the previously discussed reasons could be mitigated. Even so, gene therapy should be limited to serious conditions for which existing treatment options are poor due to the limited capacity to obtain meaningful informed consent for gene therapy experiments with significant unknown risks.

The risks of germline engineering, however, are magnified by the fact that the targeted condition has not yet manifested, and thus, the harm that will be caused by a genetic sequence can only be estimated by previous genetic correlations with phenotypic outcomes. Limitations in extrapolating the results of genome-wide association studies to particular individuals or groups not well represented in the original studies are additional cause for concern if we are to offer genetic edits as cures [27]. Furthermore, whatever unintended genetic changes occur will be heritable by future generations. As such, it should only be pursued if all previous cases demonstrate such a degree of harm that any life with this condition is not worth living and if it can be demonstrated that unintended genetic outcomes can be limited to conditions less deleterious than the target condition. This might be impossible to determine until we perform the first several human trials of germline engineering. Even if most of He Jiankui's mistakes are rectified, we must question when the risks of the next human germline editing experiment are justified.

Yet even if we can justify in terms of technical safety, these circumstances do not prevent the potential for psychological harm. Because of the infinite and undefinable ways that genetics contribute to our traits, asserting control over any part of the genome implies at least some capacity to control any other part. If an intended genetic edit successfully prevents condition X, but condition Y manifests, what prevents attempting a genetic solution to condition Y? Pursuing control of the germline will inevitably lead to an illusion of complete control that can never be realized because of the equally infinite and undefinable ways that the environment defines our experiences. As has been expressed for decades in the ethics literature on genetic engineering, this illusion could lead to a shifting health paradigm, in which traits previously seen as mere differences become diseases, and society's acceptance of difference is reduced [28]. The concomitant outcome would be an ever-increasing and inherently unsatisfiable set of expectations, likely ensuring self-discrepancy and relative depravation leading to psychological distress.

We must ask when, if ever, the risks of germline engineering would be worth taking, including the underexamined risks of psychological harm that could manifest even if the intended genetic changes are achieved. Determining when these risks can be justified must also be informed by alternatives including IVF + PGT, which can prevent the birth of a child with most currently well-understood deleterious genetic conditions. For the few conditions which IVF + PGT cannot prevent—i.e., conditions like cystic fibrosis for which there is no way to prevent the condition's manifestation if both parents have two copies of the cystic fibrosis transmembrane conductance regulator gene—the traditional alternatives are either donor gametes or adoption. For these parents, as with all parents in today's world, the traditional methods for having children promote realistic expectations for that child and the acknowledgement of its uncertain future. However, it is likely that some of these parents would not be satisfied with traditional options due to desire to have completely genetically related children free from cystic fibrosis. Another possibility is to focus greater attention on gene therapy for these conditions, so that sets of parents who are carriers of genetic disease can give birth to their genetically related children, who can then be involved in the consideration of gene therapy to treat the condition in question if they so choose. While this would not eliminate the uncertainty of outcomes and potential health/safety risks of genetic editing, it would preserve the right of the affected individual to weigh relative risks, and the psychological harm from unmet expectations could be somewhat managed by effective communication from clinician-researchers.

Because human beings deal with unmet expectations on a regular basis, it might seem that the concerns expressed here are less significant than more established ethical concerns associated with genetic engineering. But our capacity to manage the psychological effects of unexpected outcomes is correlated with an acknowledgment of having limited control. The more we believe we can control, the more serious the psychological impact of discovering one's inability to control. This can be described both in terms of the magnitude of the self-discrepancy gap and the degree of relative deprivation. A belief in control is implicit in the attempt to shape physical experience through modifying genetic code, yet because of the complexity of gene-gene and gene-environment interaction and environmental impact on physical and personality traits, such control will be undermined. Thus, the unmet expectations that will arise from unforeseen genetic editing outcomes are more profound, the self-discrepancy gap larger and the relative deprivation graver, than the unmet expectations we currently face because the expectations are higher and the actual control is inevitably lower. The resulting psychological distress will likely be exacerbated. Negative emotions,

including disappointment, depression, fear, and restlessness, affect quality of life as or more significantly than the physical states that cause the negative emotions. Ethical goals such as just access, the preservation of autonomy, or the prevention of physical harm that are at stake in a decision whether to pursue a new technology should involve at least some concern for the psychological experience of the affected individuals. Shaping the development of genetic editing with attention to the likely experience of those affected might require drawing the line short of germline engineering and ensuring effective management of expectations for those who consent to gene therapy.

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