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Revising, Correcting, and Transferring Genes

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Abstract

The distinction between germline and somatic gene editing is fundamental to the ethics of human gene editing. Multiple conferences of scientists, ethicists, and policymakers, and multiple professional bodies, have called for moratoria on germline gene editing, and editing of human germline cells is considered to be an ethical 'red line' that either never should be crossed, or should only be crossed with great caution and care. However, as research on germline gene editing has progressed, it has become clear that not all germline interventions are alike, and that these differences make a significant moral difference, when it comes to ethical questions about research, regulation, clinical application, and medical justification. In this paper, I argue that, rather than lumping all germline interventions together, we should distinguish between *revising*, *correcting*, and *transferring* genes, and I assess the consequences of this move for the ethics of gene editing.

Keywords

gene editing; germline intervention; somatic/germline distinction; mitochondrial replacement therapy

1. Introduction

The distinction between *germline* and *somatic* gene editing (like the distinction between therapy and enhancement) is fundamental to the ethics of human gene editing.[1] It is a staple of ethical discussion of gene editing that editing human germline cells – sperm, oocytes, zygotes, and other cell types involved in reproduction – raises deep and even unprecedented ethical issues not involved with editing of other human cell types. Somatic gene editing faces its own ethical issues and has plenty of critics; but the assumption that somatic and germline gene editing are not on the same page ethically, that germline gene editing ought to be subject to a higher level of scrutiny than somatic gene editing, and that germline gene editing crosses an ethical 'red line' so dramatic that the first and most fundamental question to ask about it is whether it should ever be done at all, is deeply woven into the debate over human gene editing.

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[1]This paper is the second of two essays on these distinctions; on the therapy/enhancement distinction, see Cwik 2019. For a good overview of the ethics of gene editing that gives pride of place to the role of the therapy/enhancement distinction, see Gyngell, Douglas, and Savulescu 2017

The fundamental status of the distinction and the way it shapes debate is visible in the many statements, position papers, and opinion pieces on gene editing. For example, in a recent editorial for *Science*, Jennifer Doudna, one of the developers of the CRISPR gene editing technique, wrote:

> As for medical breakthroughs, clinical trials using CRISPR are already underway for patients with cancer, sickle cell disease, and eye diseases. These and many other future uses of genome editing will involve *somatic changes in individuals*, not *heritable changes that are transmissible*. But the rapidly advancing genome editing toolbox will soon make it possible to introduce any change to any genome with precision, and the temptation *to tinker with the human germ line* is not going away. (Doudna 2019, 777; my emphasis)

Similar invocations of the distinction – of the medical potential of somatic gene editing contrasted with the ethically fraught nature of germline gene editing – are legion. The eighteen signatories of a recent call for a moratorium on germline gene editing were clear that the moratorium "does not apply to genome editing human somatic (non-reproductive) cells to treat disease, for which patients can provide informed consent and the DNA modifications are not heritable" (Lander et al. 2019, 166). The exhaustive recent report from the National Academies of Science, Engineering, and Medicine on gene editing stated that existing research ethics and regulatory protocols were sufficient for somatic gene editing (National Academies of Science, Engineering, and Medicine 2017, 6), but that germline gene editing could only be permissible if applications met a long list of desiderata (7–8). The Statement from the Organizing Committee of the Second International Summit on Human Genome Editing (2018) put it as clearly and succinctly as possible: "While we… applaud the rapid advance of somatic gene editing into clinical trials, we continue to believe that any clinical use of germline editing remains irresponsible at this time" (1).

These statements are all aimed at clinical uses of gene editing, not at research, and it is (almost) universally acknowledged that germline gene editing is nowhere near ready for clinical use. But the shape of future clinical applications will at the very least be influenced by current translational research projects on human germline gene editing, and from these projects we can get a sense of what future clinical uses in reproductive medicine may look like. From existing translational research it is increasingly becoming clear that 'germline gene editing' is not a stable category; different research projects diverge along several key dimensions, in terms of the genes they target, the intended and accidental impacts on physiology and development, and the mechanics of the procedures they utilize. These differences are not just descriptive – they substantively affect the ethical issues raised by potential applications, both in degree and kind. 'Germline gene editing' is shorthand for a heterogenous category of translational projects and possible future applications; in order to get an accurate map of the ethical terrain, we need a more precise categorization that captures the relevant idiosyncrasies of different germline interventions.

The aim of this paper is to present and argue for such a categorization schema. Rather than lumping different interventions together as 'germline gene editing' and dealing with ethical issues en masse, I argue that we should individuate interventions along four key dimensions: *target*, *goal*, *outcome*, and *mechanics*. Differences in these four dimensions will alter the

ethical issues raised by interventions, introduce new questions, take others off the table, and sharpen the importance and intensity or lessen the relevance of others. A survey of some of the key recent developments in germline gene editing research suggests grouping existing translational projects and their concomitant possible clinical applications into three broad categories: *revising*, *correcting*, and *transferring* genes. I will argue that we get a much better overall picture of the ethics of gene editing if instead of treating the somatic/germline distinction as capturing something fundamental, we instead distinguish between revising, correcting, and transferring at the germline, and deal with the unique ethical issues raised by each type of intervention.

This has significant consequences for the ethics of gene editing, which I will discuss in the penultimate section. In particular, I will argue that this raises serious doubts about the widespread slippery slope argument that crossing the ethical red line of the germline creates conceptual and normative space for increasingly exotic and troubling applications of gene editing. I will argue that this argument depends on the assumption that we cannot draw more fine grained lines of permissibility around different germline interventions by distinguishing them from each other; the framework provided in section 4 allows us to do just that, and so raises doubts about whether crossing the germline will lead us down the slippery slope. The framework also has significant benefits for other clinical and research ethics questions about gene editing, which I will briefly survey

In the next section I will discuss in more detail the somatic/germline distinction and the ethical distinctness of germline gene editing. In section 3 I will argue for disaggregating different germline interventions, and in section 4 present the framework and categorization schema discussed above. In section 5 I will assess the consequences of this for the ethics of gene editing, focusing on the slippery slope argument, before concluding in section 6.

2. The Germline as Ethical Red Line

‘Gene editing’ is an umbrella term for a wide variety of techniques and translational research projects. As it is used in the bioethics literature, ‘gene editing’ can refer to the actual act of altering a gene or the general project of altering genes for different medical (or non-medical) goals. In discussions about gene editing, genes are understood as functions, and gene editing is altering function via making changes to DNA.[2] The two parts are important: there are other ways to affect gene function (pharmaceutically, for instance) that are not considered gene editing. Editing involves not just affecting function but affecting function through the specific pathway of making changes to DNA.

The distinction between somatic and germline gene editing refers to the targeted cell type. Germline gene editing is editing of gametes, zygotes, embryos up to a certain point of embryogenesis, and (sometimes) stem cells. The National Academies report, for instance, defined the germline as “…early-stage embryos, eggs, sperm, and the cells that give rise to

[2]Thus the concept of a gene implicit in the ethics of gene editing roughly corresponds to what Griffiths and Stolz (2006) call the “postgenomic” gene, which “embodies the continuing project of understanding how genome structure supports genome function, but with a deflationary picture of the gene as a structural unit” (515). The way different concepts of the gene operate in bioethical discussion about gene editing, precision medicine, and biotechnology is an interesting and significant subject in its own right, one that is the focus of ongoing research by Reuven Brandt.

eggs and sperm" [that is, gametocytes]. 'Somatic' cells are all the rest: "…nonreproductive cell types such as skin, liver, lung, and heart cells", again in the words of the National Academies report (2017, 3). For the remainder of the paper, I will use 'somatic gene editing' and 'germline gene editing'/'germline intervention' along the lines given in the NASEM definitions.

As John Evans (forthcoming) notes, the moral reasons in favor of drawing an ethical barrier at the germline are multifarious and have changed over time. In contemporary discussion of the ethics of gene editing, three factors are key: *heritability*, *risk*, and the potential *downstream social impacts* of germline gene editing. Changes made to genes in germline cells, unlike changes made to somatic cells, can be passed to subsequent generations. With somatic gene editing, the relevant ethical questions are about gene editing as an intervention for a set of individuals suffering from a particular disease. The questions are familiar to medical ethicists – questions about clinical equipoise, risks of novel treatments, justifiable uses and medical necessity, and the like. But with germline gene editing, in addition to these questions, there are also questions about effects on future generations. Because changes made at the germline are heritable, germline gene editing introduces a novel set of risks not present with somatic gene editing. For example, in a joint statement declaring opposition to germline gene editing, the American Society for Gene and Cell Therapy (ASGCT) and the Japan Society for Gene Therapy (JSGT) cited ethical difficulties with assessing effects in future generations, uncertain outcomes given limited understanding of intragenic interactions, and deleterious effects on future generations due to limits in current gene editing technologies (namely unintended alterations of gene function due to off-target edits) as sufficiently serious risks stemming from the heritability of gene editing in germline cells to support a moratorium on germline gene editing (Friedmann et al. 2015). With somatic gene editing, risks are specifically risks to individuals. But because changes at the germline are heritable, germline gene editing introduces a different category of risks that are subject to different ethical scrutiny. Numerous statements on the ethics of gene editing have cited risks to prospective persons as reason germline gene editing requires special ethical scrutiny (Baltimore et al. 2015; Friedmann et al. 2019; Lander et al. 2019; National Academies of Science, Engineering, and Medicine 2017; Ormond et al. 2017).

In a special category of these risks to future generations are, in the words of the ASCGT/JSGT joint statement, "…the individual, familial, societal, and perhaps even species-level rights, needs, interests, and values affected by this rapidly advancing science" (Friedman et al. 2015, 1282). Though current translational research into germline gene editing is almost exclusively focused on single genes that are heavily causally relevant in the development of a class of genetic disorders (Greenfield 2018; Wolf, P. Mitalipov, and S. Mitalipov 2019), worries that germline gene editing could one day be used as a means of trait selection continue to occupy pride of place in the ethics of gene editing. Among the worries often cited in this context are the potential for germline gene editing to generate new and exacerbate existing social inequalities (Baylis 2019), negative impacts on the status of individuals with disabilities (Shakespeare 2015), and the possible selection of traits not for medical or quasi-therapeutic purposes but for biomedical enhancement (Daley, Lovell-Badge, and Steffann 2019). Some of these downstream social impacts are more realistic than others. At least one scientist has already announced an intention to pursue germline gene

editing as a means to eliminate a form of congenital deafness (Cohen 2019), underlining the potential impacts of germline gene editing on how disabilities are perceived, medicalized, treated, and accommodated. Other worries – like generating a genetic arms race through an ever-intensifying process of creating more and more enhanced children (Sparrow 2019) – depend on applications of germline gene editing that are squarely in the realm of science fiction. Yet, there is definitely interest in using gene editing for enhancement (Regalado 2019a), so worries about these sorts of downstream social impacts cannot be dismissed completely, even if for now there are other more pressing ethical issues (Cwik 2019).

For these reasons numerous advisory bodies, ethicists, and policymakers have recommended drawing a line at editing of germline cells for purposes of creating a pregnancy. How strong of an ethical barrier the germline is varies; some statements "strongly discourage" creating a pregnancy with edited germline cells (Baltimore et al. 2015), others call for outright, potentially permanent moratoria (Friedmann et al. 2015; Lander et al. 2019; Lanphier et al. 2015). There is no consensus around this; both the above-cited National Academies report and a recent report from the UK Nuffeld Council on Bioethics (2018) have stated that germline gene editing could be permissible, and the statement issued by the Organizing Committee of the Second International Summit on Human Genome Editing called for research into a "rigorous, responsible translational pathway" (2019, 2) for germline gene editing. But even if these positions stop short of considering germline gene editing impermissible, they still consider crossing the germline to be a major and ethically fraught step, one that requires intense ethical scrutiny and places it in a different category from somatic gene editing.

3. Disaggregating Germline Interventions

The issue here, however, is that not all germline gene editing is the same. Lumping interventions together masks a great deal of idiosyncrasies in the specific techniques used, and when we unpack these technical differences, we can see that there are substantial *ethical* differences between potential applications of the different techniques. To be sure, all germline interventions will have *some* common ethical difficulties. But there are substantial enough variances between different techniques and types of intervention to require a more nuanced categorization schema, and so a more nuanced map of the ethics of gene editing.

Consider the differences between the recent horrendous experiment by the biophysicist He Jiankui, and other existing translational research on germline gene editing. He Jiankui used the CRISPR gene editing platform[3] to induce a rare mutation of the gene *CCR5* (*CCR5*-Δ32) in embryos that were then used to create a pregnancy (Regalado 2018). The intention was to render both girls homozygous for *CCR5*-Δ32, which appears to have failed (Regalado 2019b). The mutation is rare, and its effects on physiology and development are not completely known. It is believed, for instance, that *CCR5*-Δ32 is involved in neurological development and specifically in memory; individuals with the mutation appear to perform better on memory tests and recover more quickly from stroke (Joy et al. 2019). *CCR5*-Δ32

[3]'CRISPR' stands for Clustered Regularly Interspaced Short Palindromic Repeats. It is a gene editing technique in which a guide RNA directs a CRISPR-associated (or "Cas") nuclease to a target.

also confers immunity to HIV infection. The gametes that were used to create the zygotes in this experiment came from an HIV positive father and an HIV negative mother. He Jiankui's stated aim was to prevent vertical HIV transmission during pregnancy, something for which there are already other good preventative options (Cyranoski and Ledford 2018).

In contrast, the few other gene editing experiments on human embryos have all focused on editing of mutations in common genes that are heavily causally implicated in the development of monogenic disorders (that is, diseases caused by a mutation in or an uncommon allele of a single gene). Researchers have explored uses of germline gene editing to target mutations in the *HBB* and *MYBPC3* genes, mutations which cause (in respective order) beta thalassemia and hypertrophic cardiomyopathy (Liang et al. 2015; Ma et al. 2017). A limited number of these experiments have been performed on human embryos, and all have been (so far) for research purposes only; no embryos have been implanted with the intention of creating a pregnancy. With all this research, the aim is, through editing, to alter the targeted genes by converting the mutated, disease-causing alleles to non-pathogenic alleles of the gene, variants that are widely prevalent in the (disease-free) population at large (Wolf, P. Mitalipov, and S. Mitalipov 2019). Given these aims the standards for evaluating the success of potential interventions is very high. There is wide agreement that germline gene editing would not be acceptable for clinical use until it is accurate enough to result in (1) removal of mutations at the edited site and (2) no off-target effects or other unintended edits so that the genome of the edited zygotes resemble – in this respect – the genome of zygotes with non-pathogenic alleles of the targeted genes.

Though both involve germline gene editing, and both are for arguably therapeutic purposes (although, as just discussed, the clinical justification for preventing horizontal HIV transmission via gene editing is virtually nonexistent), there are significant differences between the two translational projects. In the He Jiankui case, the aim was to *induce* an uncommon mutation, a mutation which could have physiological effects beyond the intended goal of the intervention and could result in ancillary impacts on the physiology of the edited subjects. In the latter set, the aim is to *remove* an uncommon mutation,[4] to alter a disease-causing genotype by replacing a pathogenic with a non-pathogenic allele of the gene, and the physiological effects are – in principle, at least – no different than the effects of having a healthy, non-pathogenic *MYBPC3* or *HBB* gene (with the caveat that there could be unintended consequences resulting from unforeseen effects of the editing procedure.). The former case thus raises a different set of ethical issues than the latter – we need to consider risks from inducing an uncommon mutation, whether any clinical rationale could justify imposing these risks, and would have to take into consideration a wider range of outcomes on prospective persons.

The differences between the He Jiankui case and other translational projects depend less on the mechanics of the procedures involved than they do on the aims, clinical rationale, and the targeted genes. This is not the case with all germline interventions; even when all these factors are, ethically speaking, on the same level, the mechanics of the interventions can

[4]This distinction between inducing uncommon and correcting common mutations and an argument for its relevance is made in Cwik 2019.

yield different ethical issues. Consider the difference between editing nuclear DNA and mitochondrial replacement therapies (MRT).[5] In MRT, mitochondrial DNA from a female donor is transferred into an oocyte from a second female. There are numerous disorders that result from mutations in mitochondrial DNA, and replacement of mitochondrial DNA in an oocyte from an individual who is a carrier for a mitochondrial disorder is one method for preventing these diseases in prospective persons (Amato et al. 2013). There are different techniques for MRT, but the overall aim is the same – to transfer mitochondrial DNA, replacing the existing maternal mitochondrial DNA with that of a third party, resulting in an individual with genetic material from three individuals – nuclear DNA from a male and female progenitor, and mitochondrial DNA from a second female.

Because MRT involves the transfer of genetic material, it raises of set of distinct ethical issues. The impacts of transferring mitochondrial DNA, and of having genetic material from three individuals, are still unknown. The limited follow-up research done on a set of children conceived from zygotes that had undergone ooplasmic transfer did not reveal any significant abnormalities or health impacts (Chen et al. 2016), but this is one study on one cadre of subjects and the monitoring involved was very limited. Individuals with nuclear DNA from two individuals and mitochondrial DNA from a third are not, for lack of a better way to put it, naturally occurring – without MRT, there would be no such individuals. There are a number of unknowns with regard to how MRT could affect development and overall health, due to the mechanics of the procedure (the incorporation of transferred mitochondrial DNA from a third party). More abstractly, there are potential ethical issues and philosophical questions about parenthood where the child is the result of genetic material from three individuals (Baylis 2013; Brandt 2016; Wrigley, Wilkinson, and Appleby 2015). Not all of these are unique to MRT – surrogacy and gamete donation raise similar issues. But the point here is that because of a technical difference between MRT and other germline interventions – that the former involves the *transfer* of genetic material from a third party – there are different ethical questions involved with the former than the latter. This does not necessarily effect permissibility; just because there are different ethical questions to ask about MRT does not mean that the bar for MRT is higher or lower. Many ethicists consider MRT to be ethically less worrisome than germline gene editing (Adashi et al. 2019). The point here is not that transfer is more ethically problematic; the point is that the mechanics of the procedure effect the ethical questions we have to ask. Presumably the questions outlined in this paragraph about transfer of mitochondrial DNA would be sharped and augmented by further issues in the (still hypothetical) case of transfer of nuclear DNA.

[5]There is significant disagreement about whether it is appropriate to put MRT in the same ethical category as germline gene editing. Baylis (2017), for instance, argues that it should be, Parens and Juengst (2001) argue that it is more complicated. The statements and position papers discussed in section 1 do not include MRT in the category ‘germline gene editing’. For purposes of this paper, this debate does not matter. If the reader is committed to the idea that MRT is in a different ethical category from editing of nuclear DNA at the germline, then the reader should take MRT as a stand in for future editing procedures that involve transfer of nuclear DNA, which is at least hypothetically possible in humans, and would be necessary for many of the kinds of exotic gene editing (for enhancement, for example) that generate so much bioethical controversy. In such cases transfer of DNA would result in an individual with a genome that they could not have via non gene editing-involved reproduction from their two progenitors (that is, they would have a genome that is not just different from what they would have had, but includes novel material than they *could not* have had, given the possible combinations from their male and female progenitors), and this would raise many of the same questions as outlined here in the discussion of MRT (for instance, questions about risks and about genetic identity and parentage). How these would relate to those discussed here about MRT is a topic for a different paper. The point here is that, whether it is mitochondrial or nuclear DNA, the mechanics of the procedure – transfer of genetic material – raises different questions that are not subsumed by those generated by other germline interventions.

In sum, though all of these are germline interventions, there are important differences between them, and these differences affect what ethical questions are relevant in assessing any possible clinical applications of the different kinds of intervention. Not all germline interventions are the same – though all of these involve editing of germline cells, the genes targeted, mechanics of the procedures, and potential outcomes are different, and this affects the ethical situation with respect to the different interventions.

4. Revising, Correcting, and Transferring at the Germline

At a coarse level of analysis, these germline interventions appear different in degree but not in kind: they all involve editing at the germline, they all have therapeutic aims, they all involve making heritable changes. The deeper look in section 3, however, reveals key differences.

1. The specific genes that are targeted makes an ethical difference. Because of the possible consequences of editing *CCR5* vs. editing *HBB*, *MYBPC3*, or mitochondrial DNA, there are potential impacts that have to do with broader effects of altering *CCR5* vs. other targets (such as potential impacts on neurological development and cognitive functioning). These differences make an ethical difference; assessing an intervention aimed at *CCR5*, for example, would have to take into account risks, long term impacts, and clinical rationale for potential larger effects on physiology and neurological development. These are different from the questions we would have to ask about a gene with a more limited impact. Because of the different impacts of mitochondrial DNA vs. nuclear DNA, and the more limited impacts of *MYBPC3* on physiology, for instance, these concerns may not be present.

2. The potential impacts on the genetic makeup and overall physiology of the individual also makes a major difference. Because mitochondrial DNA has a more limited impact than nuclear DNA on some of the more interesting traits of an individual, MRT may not raise issues that editing of nuclear DNA does. In interventions aimed at replacing a pathogenic mutation with a common, non-pathogenic variant of the gene, the result would be that any resulting individual would be – in this respect – genetically like the population at large. In the He Jiankui case, where the aim was to alter a common and healthy genotype, the resulting individuals had a genetic variation that has some unknown effects and is present in a small percentage of the population. This alters the risk/benefit calculus for the respective interventions and so raises different standards for eventual clinical justification.

3. The mechanics of the different procedures matter as well. There are specific ethical issues raised by MRT because it involves the transfer of genetic material, such as risks from as-yet unknown effects of mitochondrial transfer and ethical considerations about so-called three parent offspring. These issues are unique to MRT because it involves transfer of (mitochondrial) genetic material, and are present independently of what the intention, clinical outcome, and clinical justification is.

The upshot is, though these are all germline interventions, the different genes targeted, potential outcomes of interventions, and different techniques used all introduce different ethical questions. MRT raises complications stemming from transfer of genetic material from a third party; editing *CCR5* to confer immunity to HIV infection raises questions about risk and clinical justification involved with inducing uncommon mutations in an otherwise healthy genotype; editing aimed at removing a pathogenic mutation and replacing it with a common genetic variant avoids these sorts of issues, but still faces questions about, among other things, safety and efficacy of the editing procedure.

In order to capture the different aspects of these interventions that alter the respective level, degree, and kind of ethical scrutiny each one is subject to, we need a framework for distinguishing germline interventions from each other along the relevant dimensions. In examining the differences between these three cases, we can see that they differ from each other along four key dimensions: (1) *target*, (2) *goal*, (3) *outcome*, and (4) *mechanics* (summarized in Table 1).

Four Dimensions

Target—The specific genes or genetic material targeted creates different ethical issues for different germline interventions. The target of the intervention affects risks, clinical justification, assessment of clinical need, creates different requirements for human subjects research (this has not yet been discussed but will be argued for in section 5), and determines which applications the intervention is suitable for. Two interventions that are the same in every other respect but differ in target could nevertheless differ in ethical status. The use of CRISPR to target *HBB* vs. *CCR5* discussed above is one illustration of this.

Goal—Different intended changes in gene function also require different layers of ethical scrutiny. Even for unambiguously therapeutic applications of germline gene editing, there are significant ethical questions about clinical justification that depend on the goal. To give an example, if there are other clinical paths to achieve the same goal of a germline intervention, this affects the risk/benefit profile and possible clinical justification for the intervention. Multiple different therapeutic options already exist, for instance, for the most serious form of spinal muscular atrophy (SMA), including a neonatal gene therapy (Hoy 2019) and pharmaceutical interventions (Scoto et al. 2017). This is as opposed to, say, infantile Tay-Sachs, for which only supportive and palliative care options are available. A germline intervention targeting *SMN1* to treat SMA will therefore be assessed differently from an identical procedure that targets the *HEXA* gene to treat Tay-Sachs. There are also significant ethical questions about certain kinds of goals (choosing traits to match parental preferences, or choice of traits that could be dehumanizing or have other unacceptable downstream social impacts) that are not raised by others (altering a pathological genotype to prevent a disease).[6]

Outcome—In addition to the intended effects (the goal) of an intervention, the total suite of possible effects on an individual's physiology have to be taken into account in ethical

[6]Thanks to an anonymous referee for raising this point.

assessments. The He Jiankui case is a good example. Inducing *CCR5*-Δ32 has broader effects on an individual's physiology than just conferring immunity to vertical HIV transmission, including (as mentioned above) potential impacts on neurological development and cognitive functioning. These outcomes need to be taken into account in assessing clinical justification, risks/benefit profile, and other factors.

Mechanics—Different techniques are used by different germline interventions to alter the function of genes. In an experiment on the *HBB* gene, for instance, a team at the Sun-Yat Sen University in Guangzhou, China, used the CRISPR system to edit the *HBB* gene and repair the edited site via homology directed repair (Liang et al. 2015). The experiment had a low rate of success, resulting in embryos that were genetic mosaics, and multiple other uses of CRISPR in human and other cells have shown a very high rate of both off- and on-target mutagenesis (meaning, changes in DNA other than the targets, and unintended changes in the target), which could be pathogenic (Kosicki et al 2018). The mechanics of this procedure introduces risks involving the safety and efficacy of editing. In MRT, mitochondrial DNA from a third party is transferred, which, as discussed above, raises ethical questions not present with other kinds of editing.

Revising, Correcting, and Transferring

The examples discussed above in section 3, all drawn from the existing research on germline intervention, show that current research projects and experiments differ from each other along these four dimensions. This framework is open ended: not only existing, but also future research, can be sorted and individuated in terms of target, goal, outcome, and mechanism. But considering existing translational research projects, a natural sorting into three broad categories, suggests itself, based on how they differ from each other along these four dimensions (These three categories are summarized in Table 2). This set of groupings is provisional and will have to be revisited and surely will need to be revised as research expands and progresses. But for now, we can capture something important about the difference between the projects discussed here by grouping into these three categories.

Correcting—Most research to date on germline gene editing aims at what we can call *correcting* pathogenic mutations.[7] The target is a disease-causing mutation. The goal of the editing is to remove the pathogenic mutation and alter the gene to match a non-pathogenic allele prevalent in the (healthy) population. These experiments have shown some success in achieving this goal, but outcomes also include a continued unacceptable rate of off-target effects. The mechanism used is usually the CRISPR gene editing platform, and the use of homology directed repair or non-homologous end joining at the cleaved site. The overall intention is, as in the title of one paper reporting an important example of this kind of editing (Ma et al. 2017), correction of pathogenic mutations for purposes of preventing the development of a monogenic disease in a prospective person.

[7]'Gene correction' as a description for this sort of procedure has been used before (see, for instance, Koch 2016; Lander et al. 2019; Wolf, P. Mitalipov, and S. Mitalipov et al. 2019). Lander and others (2019) make a distinction between correction and enhancement, which is a narrower distinction than the one I am making here between correction and revision. Revising genes can include enhancement (as discussed below and in section 5), but not all revision is enhancement, as revision can also be used for therapeutic aims, as it was in the He Jiankui case (however misguided).

Revising—He Jiankui's experiment, by contrast, aimed not to correct a pathogenic mutation, but rather to *revise* an otherwise healthy genotype in line with a judgment about what, in respect to this gene, would be most valuable for an individual. Most of us have a functioning *CCR5* gene. There may be some advantages to *CCR5*-Δ32, but the goal of the editing (preventing vertical HIV transmission) can be achieved without germline intervention. The intervention thus involved a judgment that having the uncommon mutation is valuable for the individual. Since there are other means of preventing vertical transmission, this cannot be a justification for the intervention. Justification has to involve a judgment that it is *better*, all things being equal, for individuals to have a revised *CCR5* gene than not. Any future use of gene editing to select traits would likely involve gene revision. In the kinds of enhancement projects that bioethicists fret so much about, for example, otherwise healthy genotypes would be revised in accord with judgments about which genotypes are more conducive to welfare, or just generally "better".

Transferring—MRT targets pathogenic mitochondrial DNA, and in all other respects looks like a form of gene correction. However, MRT involves *transferring* of novel genetic material, genetic material that would not result from either sexual or (non-MRT) assisted reproduction. Because of this, it introduces ethical questions that are not present with gene correction in which the mechanism does not involve transfer of novel genetic material. *This does not necessarily raise the bar for justification*. Rather, it *introduces additional ethical questions*. Some of these questions were mentioned above (questions about parenthood, for example). In the next section we will consider issues about long-term follow-up in human subjects research, which differ markedly depending on whether the editing is correcting or transferring.

We have to be careful not to assume that these categories track permissibility. Whether an intervention is a correction or a transferring, for instance, does not track whether it is permissible or impermissible, or even necessarily whether it is ethically more difficult or more or less justifiable. MRT, as we've already seen, is gene transfer, but because it involves the editing of mitochondrial DNA instead of nuclear DNA, some bioethicists argue it raises less problems than would correction of nuclear DNA (Adashi and Cohen 2018). The point here is not that we can answer ethical questions merely by pointing to whether a procedure is revision, correction, or transferring, as has been assumed about whether something is a 'therapy' or an 'enhancement'. The point is that by making these distinctions and getting a more precise categorization schema, we can get a better overall map of the ethical terrain here, one which will have multiple benefits in sorting through the ethics of gene editing.

5. Consequences

Disaggregating germline interventions in terms of target, goal, outcome, and mechanism has a number of important consequences for the ethics of gene editing. The categorization schema laid out above is more accurate, and better captures the nuances of different translational research projects. But this is important because these variations track *ethical differences* between distinct sorts of germline intervention. In terms of the three factors discussed at the end of section 2 that motivate treating the germline as an ethical red line, the three kinds of intervention differ significantly. Some ethical issues will be common across

the categories; for example, all three of revising, correcting, and transferring involve making heritable changes, and so will have a common set of ethical issues stemming from heritability. But there are also different issues that arise because of the idiosyncrasies of each.

Though it is probably apparent already to the reader, risks that have to do with the downstream social effects of trait selection via germline intervention are raised more by revising than correcting genes. Correction raises significant worries about inequality in access; like assisted reproduction in general, gene correction would likely be expensive and available only to a few. This could exacerbate an already-existing gap in terms of prevalence in heritable genetic disorders between individuals who have access to assisted reproduction and those who do not (Greely 2018). But gene correction does not present the opportunity to choose traits as a means to enhance individuals to the same degree that revision would.

This argument looks very similar to the already existing proposal, made in the National Academies report (2017), to restrict germline gene editing to therapeutic applications only. This proposal assumes two things: first, that such a restriction could be enforced, and second, that the distinction between therapy and enhancement could be made clear enough to allow functional sorting of gene editing applications. If these conditions cannot be met, then crossing the ethical red line of the germline for even unambiguously therapeutic purposes appears to open the door to use of germline gene editing for enhancement. Worries of this sort often take the form of a (non-fallacious) slippery slope argument: crossing the red line of the germline for therapeutic aims creates conceptual and normative space for other uses of germline gene editing (Evans forthcoming). Since public opinion seems clearly against enhancement as an aim of germline gene editing (Blendon, Gorski, and Benson 2016), it is difficult to imagine a scenario in which people are comfortable with these applications unless they are first acculturated to therapeutic uses as part of reproductive medicine (Baylis 2019).

This slippery slope argument assumes that germline interventions cannot be disambiguated; that once any use of germline gene editing is permitted, other uses will be on the table. A major advantage of the categorization schema laid out in section 4 is that it allows us to make fine grained distinctions between germline interventions.[8] By disaggregating germline interventions in terms of target, goal, outcome, and mechanism, we can instead draw finer grained lines of permissibility based on these dimensions.

Consider the following example. A standard requirement for clinical justification for any intervention is that it aims at a significant and serious medical issue and is not in equipoise with other existing treatments. In the context of gene editing this would normally imply that there is a clear etiology from a pathogenic mutation or genotype to a significant and serious disease. Without this, it would have to be the case that intervening via altering the function of a non-pathogenic gene was in some way better than existing therapeutic options. We can thus set conditions for clinical justification as follows: either (1) the *target* must be a pathogenic mutation or genotype, and/or (2) the intervention is not in equipoise with other

[8]The utility of making fine grained distinctions for this purpose is discussed in Cwik 2019.

available treatments relative to the *goal* of the editing. (1) and (2) are minimum conditions, not sufficient; at the very least, we have to meet either (1) or (2), and if neither is met then there can be no clinical justification. Neither of these conditions were met in the He Jiankui case: possession of a functioning *CCR5* gene is not a cause of HIV infection, and there is no medical need for preventing HIV transmission via induced *CCR5*-Δ32. Conceivably, both conditions could be met by gene correction; a mutated *HEXA* gene, for instance, is the cause of infantile Tay Sachs, and altering the function via correction of the mutated gene would not be in equipoise with any other treatments (since there currently are none that prevent or cure infantile Tay Sachs). By distinguishing these two interventions via target and goal, and applying a minimal condition for clinical justification, we can draw a line of permissibility between these two germline interventions. This can generalize to a rule like the following: interventions that target non-pathogenic (otherwise healthy) genes must *at minimum* not be in equipoise with other interventions relative to the same goal. This rule could potentially permit some forms of gene correction at the germline, but would forbid applications such as He Jiankui's ham-handed attempt at genetic vaccination, among other questionable applications.[9] By making these more fine grained distinctions between the two interventions, we can thus open up just enough conceptual and normative space to cross the red line of the germline, without sliding down the slippery slope.

There are other considerations that could weigh on permissibility here. We could, for instance, draw lines around interventions that include effects on neurological development in their possible outcomes, or mechanisms that involve transfer of nuclear DNA and would potentially confer traits that an individual would not be able to have through (non-transferring) sexual or assisted reproduction. These standards would de facto forbid many of the uses of germline gene editing for enhancement that cause so much consternation, such as enhancing intelligence or giving individuals from average progenitors muscle mass or height at the long tail end of the distribution of human possibility. As an added bonus, this allows us to sidestep worries about sorting germline interventions into 'therapies' and 'enhancements', a notoriously difficult thing to do (Juengst 1997).

The categorization schema laid out here also has significant benefits for more ground floor questions about gene editing in clinical and research ethics. A major benefit of the schema is increased clarity on clinical justification, which will have benefits for eventual regulation of clinical use. For example, arguments have already been made about the different levels of risk for correction and revision. These levels of risk will factor into judgments about clinical justification. For many of the goals of translational research into germline gene editing, potential somatic gene editing interventions are currently being explored, such as research into somatic gene editing for beta thallesemia (Biffi 2018). Ethical discussion of risks from germline gene editing often cite a generic list of such risks, such as risks from off-target effects (Friedmann et al. 2015). In addition to these generic risks, as argued above, there are more fine-grained risks involved with different kinds of editing. A better map of risks from different translational projects will help weigh risks and benefits of particular germline

[9]Some would undoubtedly argue that it is too strict; the point here not that we should adopt this rule, the point is that we can formulate a rule that permits some forms of germline gene editing without inevitably leading us down the slippery slope.

interventions against somatic gene editing, and so more accurately assess any clinical justification for future, potential applications of germline gene editing.

Another important benefit concerns the vexed issue of long-term follow-up study of human subjects in clinical trials of germline gene editing (Cwik 2017, Cwik forthcoming), something that multiple advisory bodies and professional organizations have called for in any future clinical trial (National Academies of Science, Engineering, and Medicine 2017; Friedmann et al. 2015) and is part of human subjects research for MRT (Chen et al. 2016; Ishii 2019). What kind of monitoring is necessary, and for how long, depends in part on the target. Consider a use of germline gene editing that targets a mutated allele of *MYBPC3*, with the aim of preventing hypertrophic cardiomyopathy (Cwik 2020). For this target, monitoring of cardiovascular health to test the efficacy of the intervention, general monitoring of health to watch for unintended consequences as the result of the editing procedure (through, for instance, unknown and undetected off target effects), and potentially monitoring subsequent generations in order to determine whether mutagenesis occurs or deleterious off target effects are heritable is on the table. For *CCR5*, because of the many potential impacts of disabling the gene on the physiological and (possibly even) neurological and psychological makeup of the individual, much wider-ranging monitoring would need to occur, as well as watching for effects not only on subsequent generations but potentially even at the population level, in order to reach the same threshold of evidence for safety and efficacy as is the case with *MYBPC3*. This creates a bigger burden on both researchers and subjects, raises the bar that needs to be met for gene revision that involves inducing uncommon mutations, and raises the burden of justification for any clinical use.

6. Conclusion

Nothing argued for here weighs on the question of whether *we should* permit any germline interventions, be they revision, correction, or transfer. There are still huge ethical and technical issues that need to be addressed, and even if all of these are covered we may simply decide that this is a road we do not want to go down anyway. The stakes of the human gene editing debate are very high; the ethics needs to be very precise, and the framework of the ethical debate needs to evolve along with the research. The framework presented in this paper reflects innovations in translational research on MRT and germline gene editing. It is no longer tenable to lump all germline interventions together; different interventions raise different ethical issues, and issues common to all germline interventions are not relevant to each in the same degree. More precision in the overall conceptual and normative map of germline intervention enables better ethical discussion and should also put paid for once and for all to any claims that the ethics of gene editing is mired in unclear thinking and superstition.[10] Germline interventions are exciting, troubling, and potentially transformative therapeutic techniques; a better understanding of the specific issues raised by different interventions is essential for figuring out what to do about them.

[10]As alleged, for example, by Pinker (2015).

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Table 1

Summary of four dimensions along which germline interventions differ from each other, with current examples of each from the literature in last column.

Target	Specific gene or genes whose function the intervention aims to alter	*MYBPC3*[1], *HBB*[2]
Goal	Intended change in function and intended phenotypic effects	Replace *MYBPC3* with non-pathogenic allele[1], induce deletion in *CCR5*[3]
Outcome	Full suite of effects resulting from intervention, intended or otherwise	Impacts of *CCR5* on neurological development[3], potential pathogenicity of off-target effects[2]
Mechanism	What techniques are used to alter function of targeted genes	Cleaving DNA with CRISPR[1,2,3], oocyte spindle transfer[4]

Sources for examples:

[1] Ma et al. 2017

[2] Liang et al. 2015

[3] Regalado 2019b

[4] Zhang et al 2017.

Table 2

Summary of three kinds of current translational research projects.

	Revising	**Correcting**	**Transferring**
Target	Varies	Disease-causing mutation	Varies
Goal	Varies	Remove pathogenic mutation or genotype	Varies
Outcome	Includes change in otherwise non-pathogenic genotype	Goal + off-target effects	Varies
Mechanics	Involves no introduction of novel genetic material	Involves no introduction of novel genetic material	Involves introduction of novel genetic material
Example from Literature	Regalado 2019b	Ma et al. 2017, Liang et al. 2015	Zhang et al. 2017

Citations in final row refer to published or reported experiments that serve as paradigmatic examples of the three categories.