The Ethical Gene

Introduction

Recent technological advances and rogue human experimentation make strikingly clear the need for ethically sound regulation governing the genetic modification of the human germline.[1] Currently there is a growing consensus amongst scientists that a temporary moratorium on such interventions is warranted.[2] This view is widely shared by policy makers and legislatures. Indeed, many jurisdictions have enacted laws that aim to prohibit individuals from intentionally introducing inheritable modifications to the human genome.[3] While well-intentioned[4] the approach currently taken by both the scientific community and many legal jurisdictions in crafting their laws is problematic. In both cases particular uses of 'genetic modification' are imported from scientific practice and, I argue, these uses are inappropriate for the ethical and regulatory ends they are meant to serve. Drawing from legal and policy examples I will show that current approaches (1) are over-broad, (2) fail to take into account our evolving understanding of biological inheritance, and (3) mask what is ethically relevant about genetic modification. Instead, I argue we should develop ethical criteria for conscribing reproductive interventions that may affect future generations

[1] Cyranoski, D. (2019). The CRISPR-baby scandal: what's next for human gene-editing. *Nature* 566(7745). 440–443.

[2] Dyer, O. (2019) Scientists call for moratorium on editing heritable genes. *BMJ*. 364:l1256.

[3] van Beers, B. (2020) Rewriting the human genome, rewriting human rights law? Human rights, human dignity, and human germline modification in the CRISPR era. *Journal of Law and the Biosciences*. 8(1).

[4] Even for those with a positive view of germline genetic modification's long-term prospects, there is much to be said about pausing to take stock of the current state of the science and taking time to craft appropriate safeguards.

and apply these to emerging technologies. In short, we ought to move away from employing particular scientific uses of 'gene' for drawing normative boundaries and instead employ more appropriate normative concepts for determining where to draw ethical lines. In the final section of the paper I will outline a suggestion for what an `ethical' gene might look like.

1 The 'Regulatory Gene'

Philosophical literature examining the ethics of germline genetic modification generally pays little attention to what constitutes a gene. This leaves the false impression that the extension of the term is more or less fixed and that its extension is unambiguous. But in fact what constitutes a gene has changed greatly since the term was first introduced by Wilhelm Johannsen in 1909, and determining its proper extension remains a matter of debate. Johannsen's definition was quite broad, encompassing whatever elements of gametes shape an organism's phenotypic characteristics. According to Johanssen, "The word gene is completely free of any hypothesis; it expresses only the evident fact that, in any case, many characteristics of the organism are specified in the germ cells by means of special conditions, foundations, and determiners which are present in unique, separate, and thereby independent ways".[5] Subsequent developments in biology located genes on chromosomes and identified genes with the sequences of DNA bases that encode proteins. This definition of the gene, sometimes referred to as the 'molecular gene', persists in many contemporary textbooks and is a fall back often offered by biologists when pressed for a definition.[6] But further discoveries have revealed that many non-coding segments of DNA that were initially declared "Junk DNA" are in fact important for gene expression and protein synthesis, and hence for determining phenotype.[7] Indeed there are many features of the transmission of traits via DNA that belie the molecular

[5] Johannsen, W. *Elemente der exakten Erblichkeitslehre*. Gustav Fischer, 1909. As translated in, Portugal, F. H., & Cohen, J. S. (1977). *A Century of DNA: A History of the Discovery of the Structure and Function of the Genetic Substance*. Mit Press. p 118.

[6] Griffiths, P and Neumann-Held, E. (1999)The many faces of the gene. *BioScience* 49 (8) 656–662.

[7] Fox Keller, E. From gene action to reactive genomes. (2014) *The Journal of Physiology* 592(11). 2423–2429.

gene. For instance, DNA sequences far apart from each other can interact in ways that affect an organism's phenotype. Consequently, it is not easy to clearly delineate where DNA sequences that constitute genes begin and end.[8]

Additionally, we have discovered that DNA base-pair sequences are not the sole biological mechanism contained within gametes for encoding traits to be transmitted to future progeny. There is strong evidence that a host of other factors, including DNA methylation, histone structure, and non-coding RNAs play a role as well. These mechanisms of phenotypic inheritance which do not involve variations in base-pair sequences are often called 'epigenetic' or 'non-genetic' forms of inheritance.[9] I will have more to say about epigenetic inheritance later, but for now it is worth noting that it is unclear whether the term 'gene' as currently conceived ought to encompass mechanisms of inheritance other than DNA base-pair sequence. Johannsen's more expansive definition of the term would certainly include methylation, histone structure, and non-coding RNA, since these are all mechanisms of inheritance contained within germ cells. Indeed, some argue that the distinction between genetic and epigenetic/non-genetic inheritance reflects nothing more than the order of discovery and established scientific conventions.[10]

All this to say that the extension of the term 'gene' is very much a matter of scientific and philosophical dispute. Policies thus cannot simply prohibit interventions that result in potentially transmissible genetic modifications without some further specification. Furthermore, restricting all interventions that result in changes to traits encoded by gamete-mediated processes would exclude too much to be plausible. Diet and stress all have epigenetic effects[11] and yet restricting individuals from making changes to aspects of their lifestyle for the sake of preventing 'genetic' modification of offspring is clearly problematic for a host of reasons.

In order to avoid these disputes, influential policy governing germline genetic modification tends to focus on alterations to the DNA of germ cells.

[8] Phillips, P. (2008). Epistasis—the essential role of gene interactions in the structure and evolution of genetic systems". *Nature Reviews Genetics* 9(11). 855–867.

[9] Skvortsova, K, Iovino, N &Bogdanovi´c, O. (2018) Functions and mechanisms of epigenetic inheritance in animals. *Nature reviews Molecular cell biology* 19(12) 774–790.

[10] Keller, op. cit note 7.

[11] Skvortsova & Bogdanovi´c. op. cit. note 9.

For instance, at the 2015 Napa meeting of scientists, legal experts, and ethicists convened to discuss genome engineering technologies, the term 'germline modification' was taken to mean "changes in the DNA of the nucleus of a germ cell".[12] The participants recommended that inducing any such changes in human beings should be strongly discouraged. Similarly, the Canadian Assisted Reproduction Act prohibits procedures that "alter the genome of a cell of a human being or *in vitro* embryo such that the alteration is capable of being transmitted to descendants"[13], and defines the genome as the "the totality of the deoxyribonucleic acid [DNA] sequence of a particular cell".[14] Similarly, the UK Human Fertilization and Embryology Act 1990 prohibits fertility treatments involving the in vitro creation of embryos that employ anything other than 'permitted' sperm and eggs. For the purposes of the act, sperm and eggs refer to cells of the male and female germline respectively, at any stage of development. To be permitted these cells must have been produced or extracted from testicles or ovaries, and not had their nuclear DNA modified.[15]

For regulatory purposes then, a common approach is to restrict the meaning of germline genetic modification to the modification of the DNA of germline cells. At first blush this approach may appear attractive. It provides concrete guidance about what is impermissible —altering the DNA of germ cells that will be used in certain reproductive procedures —without having to wade into debates in theoretical biology and philosophy of science about the nature and extension of genes. Furthermore it restricts the use of recent technological interventions that modify DNA that many find alarming (such as Crisprcas9, TALENs, and engineered viruses) without restricting more banal activities that may affect inherited phenotypic traits to future progeny, such as diet and exercise. But the attractiveness of this approach quickly fades when we examine what it entails while taking into consideration the complex biological details of sexual reproduction.

[12] Baltimore, D, Berg, P, Botchan, M, Carroll, D, R. Charo, R.A., George Church...Greely, H.T. (2015). A prudent path forward for genomic engineering and germline gene modification. *Science* 348(6230). 36–38.

[13] Assisted Human Reproduction Act (S.C. 2004, c. 2) §5(1)

[14] Ibid §3

[15] Human Fertilisation and Embryology Act 1990 §1 and §3ZA

2 Regulatory Genes Meet The Birds and the Bees

Many of the problems that belie the current regulatory approach arise because of inattention on the part of ethicists and regulators to the fine-grained biological details of sexual reproduction, and gamete formation in particular. On close inspection of these details, it turns out that many uncontroversial medical interventions alter the DNA of germ cells that then go on to produce offspring. Prohibitions on medical interventions that alter the DNA of gernmline cells, including the more nuanced regulations enacted in the UK end up bring grossly over broad.

Consider first relatively uncontroversial interventions like *in vitro* fertilization (IVF) and intracytoplasmic sperm injection (ICSI). Both are medical procedures that aim to induce fertilization outside of the body in an artificial environment designed to promote the early stages of zygotic development. But these procedures do in fact result in dramatic changes to the DNA of germ cells. This fact is often overlooked, likely because the processes of gamete and zygote formation are often described in simplified terms. Human fertilization is often depicted as the union of an ova and sperm, each of which contains half the DNA compliment necessary for the development of a new human being. And ovulation is often described as the process in which one or more ova containing half the DNA compliment necessary for reproduction are released as part of the menstrual cycle. But in fact fertilization and ova formation are much more intertwined than these simplified pictures suggest. To see how, we need to take a closer look at meiosis - the process by which gametes are produced from somatic cells.

Meiosis involves two cellular divisions, each of which results in cells with half the DNA of their progenitor. The cell that forms after the first meiotic division is called a secondary oocyte (also called a mature oocyte). This cell has twice the DNA compliment of an ovum, and is the cell released during menstruation. An ovum forms following the second meiotic division, which is triggered by interactions between sperm and the secondary oocyte. Once this second division occurs, DNA can then be incorporated into the nucleus of the

ovum and the zygote can develop. This is why ova formation and fertilization are intertwined. [16]

The maternal portion of the genome inherited by the zygote is thus modified by IVF and ICSI, because these procedures trigger the completion of meiosis –a biological process in which the genome of cells is altered. These biological details are clearly important given the regulatory focus on 'alterations to DNA'. The reason is that a prohibition against all medical interventions that result in transmissible modifications to the nuclear DNA of germline cells, like that proposed at the Napa meeting and that contained in the Canadian legislation, unwittingly prohibit these relatively uncontroversial procedures. Indeed, if taken literally, regulations that apply outside of the medical context, like that found in the Canadian legislation prohibits 'natural' sexual reproduction as well. After all, these same changes to DNA occur *in vivo* as part of the fertilization process.

This is of course not what regulators and policymakers intend. Regulators and policymakers seek to proscribe *certain kinds* of alterations to the DNA of germ cells —presumably those that are 'unnatural', 'artificial' or meet some other similar criteria. But attempts to specify by reference to biological categories where the lines ought to be drawn is fraught with difficulties that makes the problem of over breadth difficult to escape. For instance, we might point to the UK legislation described above as better indicative of what is intended. This legislation prohibits the implantation of embryos created *in* vitro from germ cells whose DNA has been altered prior to fertilization, but does not restrict modifications to DNA that arise as a consequence of the normal processes involved in fertilization. This is likely more in line what individuals have in mind. We might think that putting gametes in close proximity or contact with each other and then letting nature take its course is importantly different from administering substances that cause changes to DNA. But even this more nuanced approach, if taken literally, would prohibit many fertility treatments generally considered uncontroversial. IVF following in vitro ovarian maturation and IVF following ovulation induction are both ruled out by a strict literal interpretation of this legislative approach, as they involve altering the nuclear DNA of germ cells prior to fertilization.

[16] Jones K.T., Lane S.I.R., & Holt J.E. (2013). Start Stop Signals of Oocyte Meiotic Maturation. In: Coticchio G., Albertini D., De Santis L. Oogenesis (pp183-193). Springer, London.

To see why, we need to take a further look at the biological processes leading up to the first meiotic division. The process of ova formation begins *in utero* but pauses prior to the first meiotic division, then resumes puberty. At puberty, hormonal signals stimulate the resumption of meiosis, which results in the formation of one or more secondary oocytes in each menstrual cycle. As noted above, the first meiotic division results in a secondary oocyte containing half the DNA present prior to the division. The remainder of the DNA is contained in a smaller cell called a polar body that is reabsorbed by the body. It is the secondary oocyte that is released during the menstrual cycle, and if fertilized can go on to produce an ovum and a zygote.[17]

This picture differs greatly from the more simplified description of ova formation that is often presented roughly as follows: "The full complement of ova form while the foetus is still *in utero*. At sexual maturity usually one ova though sometimes more are released as part of menstrual cycle."

This common simplified description gives the false impression that ova fully form *in utero* and that during the menstrual cycle one or more of these eggs are simply released. Crucially, it obscures the fact that ovulation involves the completion of a meiotic cellular division, which results in the reduction of DNA in cells of the germline. Again, this detail is important given the regulatory focus on prohibiting alterations to the DNA of cells. It shows that substances administered to stimulate ovulation do not merely cause the release of ova that have already fully formed and are awaiting release. Rather, stimulating ovulation triggers the completion of the first meiotic division, a process that reduces the amount of DNA present in germline cells.

Interventions of this sort are commonplace and widely accepted. For instance, hormones are used as part of IVF procedures in order to stimulate ovulation so that many secondary oocytes can be collected at once. Similarly, hormones are used in *in vitro* maturation of ovarian tissue to create secondary oocytes that can then be used in IVF. These widely practiced medical interventions cause cells of the germline to divide in a manner that causes them to lose half their DNA. This is clearly causing a change to the DNA of germ cells. These germline cells are then used to create embryos in vitro, which are then implanted. Consequently, a literal reading of UK legislation, which prohibits implanting embryos that were created in vitro from germ cells that have had their DNA altered poses problems for procedures that rely

[17] Ibid.

on such techniques.[18] Less nuanced regulations like that proposed at the Napa meeting and that contained in the Canadian Assisted Human Reproduction Act also rule out these techniques. After all, they result in inheritable alterations to the genome of germ cells.

At this stage one might think that we could simply patch existing regulations by being more precise about what we mean by 'modification of DNA'. For instance, we might point to the fact that meiotic division is a natural process and that base pair sequences are not altered. There is a loss of DNA, but no change to the bade-pair sequences that make up chromosomes. We might thus define 'alteration to the nuclear DNA of germ cells' as the creation of novel base-pair sequences not originally found in the germline cells in question.

Interpreting the modification of DNA in this manner would make permissible the kinds of fertility treatments discussed above, but it results in other problems. For one, it would mean that fertility treatments similar to the ones discussed above but provided to men would be impermissible. To see why, we need to take another closer look at the underlying biology. In men the entire process of meiosis takes place following the onset of puberty. One of the mechanisms for increasing genetic diversity, chromosomal crossover, takes place during the early phases of meiosis, antecedent to the first meiotic division. When chromosomal crossover occurs paternal and maternal chromosomes swap portions of their DNA. This results in 'daughter chromosomes' that have distinct base-pair makeups from the chromosomes from which they were derived. Each chromosome that undergoes crossover contains both paternally and maternally derived base-pair sequences. This is a process sometimes described as 'reshuffling the genes'.[19] When drugs are

[18] It is worth noting that there is an ambiguity in how to interpret the HFE Act that is relevant here. The HFE Act prohibits the implantation of embryos created in vitro other than those created via permitted sperm and eggs. The act further defines a permitted egg as one "(a) which has been produced by or extracted from the ovaries of a woman, and (b) whose nuclear or mitochondrial DNA has not been altered". It is unclear if this clause should be read as prohibiting the use of eggs whose DNA has been altered after extractions, or if it should be read as prohibiting the use of eggs whose DNA had been modified at any time. If the latter is the correct the IVF following ovulation induction is permissible. However, it remains that in either case IVM is prohibited since the alterations to the genome that occur as part of the maturation of ovarian tissue occur in vitro.

[19] Jeffreys, A & Neumann, R. (2002) "Reciprocal crossover asymmetry and meiotic drive in a human recombination hot spot". *Nature genetics*. 31(3) 267–271.

administered to stimulate the production of sperm, one effect is thus the creation of novel base-pair sequences that result from crossover in meiosis.[20] Refining the definition of 'genetic modification' to mean changes in base-pair sequence is thus still over-broad in that it would prohibit this non-controversial medical treatment. In the UK context it would mean that sperm produced in this manner could not be used for the purposes of IVF.[21]

Putting aside this concern, a second problem with moving the focus to changes in base-pair sequences is that, depending on one's views, it may permit too much. For instance, it would permit individuals to exercise control over the particular combination of chromosomes sourced from primordial germ cells to be used in creating an embryo. Mixing and matching chromosomes would not require any alterations to base-pair sequences, but doing so could have a substantial effect on the traits of offspring. It would allow individuals to ensure that their offspring either inherit or avoid inheriting certain genetic sequences associated with particular phenotypic traits. For instance, reproducers could use this technique to ensure their offspring do not become asymptomatic carriers of a recessive genetic disorder, or suffer from a dominant genetic disorder. Reproducers could also use this technique to ensure that sequences associated with eye colour, height, and other traits were transmitted to offspring. While reproducers would have a limited palette available to them —they would be limited to those sequences present in the primordial germ cells selected —they may still have considerable control over the genotype and phenotype of offspring. Those who object to germline genetic interventions on the basis that it is wrong to exercise fine-grained control of the traits of one's offspring would likely find such interventions problematic. It should be noted that the ability to exercise control over the chromosomal makeup of embryos is not mere science fiction. Technology to enable to enable such control is already under development and has been tested in animal models. Indeed, use of such technologies have already been proposed as a potential treatment for some chromosomal disorders.[22]

[20] The particular combination of sequences constituting the chromosome is novel.

[21] "This rests on a similar ambiguity in interpreting the HFE Act as mentioned in footnote 18. Compare to HFE Act 3ZA (3)".

[22] Paulis, M., Castelli, A., Susani, L., Lizier, M., Lagutina, I., Focarelli, M. L., ... & Vezzoni, P. (2015). Chromosome transplantation as a novel approach for correcting complex genomic disorders. Oncotarget, 6(34), 35218.

We might draw a distinction between the use of hormones for stimulating spermatogenesis (or gameteogenesis more generally) and chromosomal selection by arguing that the former restores 'natural' gonadal functioning while the latter employs medical technology to determine the genetic attributes of offspring. In one sense, such a move would be an improvement. Drawing the distinction in this manner moves away from drawing ethical lines by designating certain biological structures as normatively unalterable. In so far as my critique is focused on the pitfalls of using biological categorizations for delineating ethical lines, this is a move in the right direction. But appealing to nature is this manner is unlikely to be successful. While appeals to nature and 'normal functioning' are common in many bioethics debates, [23] they are not without their significant and well documented shortcomings. While I will not rehearse all the arguments here, I will note two serious challenges that such an approach would face. First, as demonstrated by John Stewart Mill, the distinction between the natural and the non-natural is itself fraught. [24] We are biological creatures crafted by nature to be able to exercise control over ourselves and our environment. It is thus unclear why technological control over reproduction is any less natural than say a beaver's control over their environment. Second, appealing to normal species functioning may well permit too little. For instance, it may prohibit providing fertility treatment to those suffering from age-related fertility decline, since such a decline is part of normal species functioning. To restore fertility would be to create an unnatural state of affairs that departs from normal species functioning.

Finally, it is worth noting that there is some evidence suggesting that fertility treatments including IVF may increase the rate of *de novo* mutations in offspring.[25] It is not clear whether this increase in mutations is due to the fertility treatment themselves [26] but if they are, this would pose further regulatory problems even if the health consequences prove relatively minor

[23] Debates about enhancement vs treatment and the scope of necessary medical treatment are two examples.

[24] John Stuart Mill. *Nature, the utility of religion and theism*. Vol. 19. Watts, 1904.

[25] For example, see Zheng, Ying-Ming, et al. "Alterations in the frequency of trinucleotide repeat dynamic mutations in offspring conceived through assisted reproductive technology." Human reproduction 28.9 (2013): 2570-2580.

[26] Berntsen, Sine, et al. "The health of children conceived by ART:'the chicken or the egg?'." Human reproduction update 25.2 (2019): 137-158.

and/or within acceptable risk parameters. This is because such mutations would be 'unnatural' and would occur in the creation of *in vitro* embryos.

The preceding discussion is not to suggest that IVF, *in vitro* maturation of ovarian tissue or other similar interventions ought to be prohibited because they involve altering germline DNA. Nor should we conclude that since we have already 'crossed the Rubicon', all DNA modification is fair game. What I seek to show is that current practice is in tension with current regulatory frameworks and that much of this tension arises because of inadequate attention paid to the ways in which standard medical treatments alter the DNA of germ cells. The takeaway is that drawing ethical boundaries by designating certain biological structures as normatively unalterable is unlikely to succeed. If we use the totality of a gamete's nuclear DNA as the operational definition of its genes, then the appropriate regulatory question is *which* germline genetic modifications we ought to permit, not whether we should permit them at all. Prohibitions on modifying the genome of germ cells of the kind often cited in policy and regulation need to be abandoned in favour of more nuanced regulation that looks at features other than the kind of biological structure being altered. Crucially, this shift is necessary given *current* widely embraced practices and not just because of anticipated technological developments that lie on the horizon.

2.1 Why just DNA?

Even if we could find biological criteria that would successfully narrow the scope of 'DNA modification' so as to avoid the problems of over-breadth we would still be faced with another problem: how to justify the focus on nuclear DNA. This is because, as noted earlier, DNA is not the sole medium involved in the inter-generational transmission of phenotypic traits. A singular focus on DNA is defensible only if we can point to significant ethically relevant differences between DNA-encoded traits and those influenced by epigenetic mechanisms. Until recently scant philosophical attention has been paid to the place of epigenetics in debates about alterations to inheritable traits. However, recent work by Tim Lewens convincingly demonstrates that the ethical importance placed on the distinction between epigenetics and

genetics is difficult to sustain.[27] Consider two general categories of potentially salient differences between epigenetic and DNA-encoded traits that might be ethically significant: (a) facts about the transmitted traits themselves, and (b) pragmatic concerns raised by the potential implementation of regulation. Factors relevant to (a) include the kinds of traits in question, the extent to which they are inheritable, and their intergenerational stability. Factors relevant to (b) include the invasiveness, feasibility, and unintended harms of potential regulation. Leaning on Lewin's work, in what follows I will argue that even though epigenetic mechanisms of inheritance do differ from DNA-encoded traits with respect to both (a) and (b), these differences cannot justify strict regulation in the case of the latter.

First let us consider concerns falling within (a). Those who seek to limit the scope of regulations governing inheritable genetic alternations to those that involve nuclear DNA often draw a distinction between 'personal characteristics' and other kinds of inheritable traits. Personal characteristics are traits that make an individual 'who they are'.[28] They are traits that are important for individuals' self-conception, and affect how individuals relate to others and the world. Such traits can be contrasted with those that are widely shared, are of little significance to an individual's self-conception, or whose normal range of variation have inconsequential effects on how an individual leads their life. For example, perfect pitch is personal characteristic, while a difference in the rate of perspiration that is undetectable outside the laboratory is not. Many personal characteristics like height, hair colour, eye colour, propensity for athletics, personality, and intelligence, are influenced by variations in DNA. Indeed nuclear DNA is often referred to as an organism's 'blue print'.[29] By contrast, inherited epigenetic variations are thought to play a lesser role in determining personal characteristics, and are largely associated with the presence or absence of disease. We might thus think that it is predominately DNA that makes an

[27] Lewens. T. (2020) Blurring the germline: Genome editing and transgenerational epigenetic inheritance. *Bioethics* 34(1) 7–15.

[28] For a discussion of the role of personal characteristics in debates about genetic modification see, Brandt, R. (2016). Mitochondrial donation and 'the right to know'. *Journal of medical ethics*, *42*(10), 678-684.

[29] This is not to suggest that genes are the sole player in the development of characteristics. For a good discussion of the role of the environment in development see chapter 7 of Lewens, T. *The biological foundations of bioethics*. OUP Oxford, 2015.

individual 'who they are', and this justifies the special importance placed on DNA.

This distinction is not without its criticisms. It is unclear why inherited diseases or predisposition to such diseases ought not count as personal characteristics. After all, suffering from a disease or having a predisposition to do so often affects an individual's self-conception, the way they relate to others, and affects the way they lead their life.[30] More thus needs to be said for why disease and predisposition to disease ought to be excluded from the traits that count as personal characteristics. Furthermore, there is still much that is unknown about the range of phenotypic traits that are influenced by epigenetic mechanisms. But even if we accept that nuclear DNA is uniquely central to the development of personal characteristics, this would not justify policy that prohibits alterations to all nuclear DNA yet remains silent about epigenetic modifications. This is because many DNA sequences do not encode personal characteristics. Some regions of nuclear DNA are associated only with the presence or absence of disease, or with non-pathological variations that make no difference to any personal characteristics. In terms of the kind of traits encoded, then, such sequences are similar to epigenetic variations. Placing special importance on the inheritance of personal characteristics thus cannot justify a blanket prohibition on all alterations to nuclear DNA, while remaining silent about epigenetic means of inheritance.[31]

The second argument for justifying the distinction between traits encoded by epigenetic mechanisms and those encoded by nuclear DNA is that alterations to nuclear DNA have greater intragenerational stability. While some epigenetic alterations demonstrate limited intergenerational stability, it remains unclear whether effects last beyond three or four generations. By contrast, alterations to the nuclear genome are much more permanent, at least in the absence of subsequent interventions. We might naturally think that the greater permanence of alterations to nuclear DNA warrants special concern and so justifies the ethical and regulatory focus on nuclear DNA. But as noted by Lewens, there are two reasons to reject this argument. First, the very technologies prompting the move towards tighter regulation, like

[30] Bredenoord, A Dondorp and Guido Pennings make this point in relation to the standing of mitochondrial DNA. See Bredenoord, A, Dondorp, G & Pennings, G. (2011) Ethics of modifying the mitochondrial genome. *J Med Ethics* 37(2) 97–100.

[31] Lewens, op. cit. note 21.

CRISPR, have the potential to make modifications to nuclear DNA easily reversible.[32] Second, many of the ethical concerns raised in response to the spectre of genetic modifications do not derive their force from the possibility that modifications will persist for many generations. For instance, many of the ethical concerns raised by the prospect of creating offspring with specific aptitudes (intelligence, athletic ability, musical talent, etc.) rest on the damage done the parent-child relationship, and the harm offspring might experience as a result of learning they were engineered by their progenitors. Such harms would not extend to future generations, unless producing further offspring with these traits was what motivated subsequent reproduction.

We can then turn to pragmatic concerns about regulation. We might think that regulating alterations to the epigenome would be both undesirable and impracticable. After all, the epigenome is affected by a host of environmental and lifestyle factors, including diet, exercise, stress, and pollution. It is not possible for individuals to prevent the transmission of epigenetic changes to their offspring. Furthermore, epigenetic mechanisms play an important role in phenotypic plasticity by modulating gene expression in response to features of the environment, which is important for the well-being of organisms. The transmission of traits through variations in the epigenome is a normal part of organism functioning. We might thus think that any attempt to regulate epigenetic alterations risks imposing overly burdensome restrictions on regular activities and interfering with normal biological functions. But on reflection, similar concerns arise in the case of alterations to nuclear DNA as well. Exposure to environmental toxins and increased age, especially paternal age, both increase the risk of *de novo* genetic mutations in gametes. Restricting all activities that may lead to genetic alteration would thus likely be overly burdensome. Furthermore, chromosomal crossover, which, as stated, is a normal part of meiosis, results in alterations to the nuclear genome of gametes. Indeed, genetic mutations are a normal part of species evolution. Taking aggressive steps to prevent all genetic alterations to germ cells would interfere with normal biological functioning.

These concerns do not make regulation impossible. The preceding discussion simply shows that we must be specific about the kinds of alterations we permit and prohibit. This is true of both genetic and epigenetic modifications. For instance, we might choose to prohibit transmissible

[32] Ibid.

modifications created via means of medical technologies that aim to enhance offspring's capabilities beyond the normal range of human functioning while remaining silent about changes to inheritable traits that arise due to environmental effect. Such regulation could apply equally to epigenetic and genetic mechanisms of inheritance. The main point is that natural plasticity of the epigenome poses no special pragmatic challenge for regulation.

3 The Path Forward

So far I have argued that the current practice of designating a certain biological structure, namely the DNA of germ cells, as normatively unalterable for the purposes of certain reproductive interventions is problematic. Paying close attention to the underling biology reveals that this strategy is overly broad in that it prohibits medical interventions that are not controversial. Furthermore, the focus on DNA ignores epigenetic mechanisms which also play an important role in the inter-generational transmission of phenotype. At a minimum, the singular regulatory focus on DNA warrants a more detailed defence. And upon reflection, it should not be surprising that we run into trouble when we expect biological categories to map neatly onto ethical categories. This is because the normative standing of an action is determined by a host of factors including the intentions of the actor, the act's likely consequences, and the presiding legal and social norms. Though features of normative evaluation arguably do influence how we divide up the natural world, I take it as uncontroversial that scientific classification does not seek to capture moral features when 'carving nature at the joints'. It would thus be an astounding coincidence if scientific categorization also provided clear normative guidance.

Of course, sorting out the normative factors that undergird the permissibility of germline genetic modification is complex. While there is widespread agreement that germline genetic modification is morally fraught, there is a wide diversity of views about what justifies the moral concern. For some the major barrier is at its core technical. On this view, the current state of technology and our understanding of genetics renders the use of currently available tools too dangerous to be permissible. However, these barriers are surmountable and in the future genetic modification may well be permissible. Others argue that intentionally altering the germline is intrinsically wrong.

Yet others worry that genetically engineering offspring will exacerbate inequalities, alter the way we view our offspring, change the way children view themselves, or open the door to potential abuse that will be impossible to constrain. Not all these arguments prohibit all kinds of genetic modification in all cases. For instance, those who see intrinsic value in the 'natural' human genome might find interventions that revert induced alteration unproblematic or at least acceptable in some cases. Similarly, those who are worried about unforeseen consequences of genomic manipulation might think that replacing a pathological genetic sequence with an existing sequence known to confer health is permissible in some cases, but that the introduction of artificial genes ought to be prohibited. Indeed recent work by Brian Cwik outlines why drawing fine grained distinctions between different kinds of genetic manipulation is normatively important.[33]

But that the underlying moral questions are yet to be resolved does not mean that we ought to turn to scientific categorization to serve regulatory and policy needs. An alternative is to create an ethical relevant definition of the gene that captures the scope of reproductive interventions in need of special ethical consideration. This definition may depart from how the term is employed in a scientific context and well may for example be broad enough to include epigenetic mechanisms as well. For instance we might define the ethical gene as "any physical structure contained within an organism with the potential to impart phenotypic traits to multiple subsequent generations". Once the bounds of the category have been set, we can then assess on an individual basis what kinds of genetic modification to prohibit and what kinds to permit. This approach in some sense lacks the clarity and simplicity of the current near categorical ban but has three distinct advantages. First, it makes explicit what is in fact current practice. As I have shown in the preceding sections, it is simply not true that we prohibited all germline genetic modification, or that we prohibit the implantation of embryos created *in vitro* from gamete who's DNA has been altered. Furthermore, such prohibitions, if enforced would in fact be undesirable. We cannot escape the need for assessing particular interventions on their own merits. Second, it forces regulators and policymakers to examine the normatively relevant features of a proposed intervention rather than the scientific classification of

[33] Cwik, B. (2020). Revising, correcting, and transferring genes. *The American Journal of Bioethics* 20(8) (2020), 7–18.

the biological structures involved. It is worth noting that in the debate about the permissibility of mitochondrial replacement techniques, much ink was spilled debating whether the mitochondiral genome was or was not part of the germline. Such debates about classification add little to our understanding of the important moral questions at hand, yet are encouraged by the current regulatory schema. Finally, adopting a definition of gene fit for ethical purposes means that changes to our scientific understanding of the transmission of traits need not necessarily require a reassessment and retooling of the ethical guidelines in place. The current narrow focus on DNA leaves out biological mechanisms known to be involved in the transmission of traits and it is likely that other such mechanisms exist as well. While such a move might seem radical, it is in fact more in keeping with the original use of the term 'gene', as noted at the outset of the paper.

This proposal is not without its possible downsides. One major drawback is that it would mean that ethicists would be using terminology in a different manner from those working in the very disciplines that are the subject of the ethical analysis. This may make interdisciplinary communication and collaboration more difficult. Furthermore, policy makers and members of the public understand 'gene' in much the same manner as scientists. Using the same terminology in a bespoke sense thus might make influencing regulations, engaging the public, and other important endeavours more challenging. To this I have two responses. The first is that this problem is not new. Philosophers engaging with the law often use terms such as 'responsibility', 'consent' etc. in ways that depart from their stricter legal meanings. So long as interlocutors specify how they are using the terms in question interdisciplinary communication can (and indeed does) thrive. Secondly, for those who find this response too pollyannish there is alternate path forward. Ethicists could adopt an alternate term to designate mechanisms of inheritance contained within gametes, such as 'GMIs' for example. The term 'gene' as used by scientists would be an example of a GMI. This way there would be no confusion resulting from the same term being used in multiple ways by different disciplines, and a broader term that avoids the shortcomings of the current use of 'gene' would be available. Space constraints do not allow a full assessment of the merits and demerits of these two proposals. What is clear, however, is that we must move beyond the narrow normative focus on alterations to DNA.

4 Conclusion

In this paper I have argued that current law and policy governing germline genetic modification is overly broad and in fact prohibits medical interventions normally considered unobjectionable. The root of the problem lies in the fact that law and policy tend to espouse bans on medical interventions that alter germline DNA. However, if we play close attention to the biological mechanisms at play we see that many standard medical interventions result in alterations to DNA that can be transmitted to future generations. The correct focus of policy and regulation thus ought to be determining which kinds of transmissible genetic modifications ought to be permitted, and not whether they should be permitted at all. Given that the scientific classification of biological structures involved in the inheritance of traits is unlikely to be in itself ethically significant, ethicists ought to develop a definition of gene fit for ethical purposes, or else develop alternate terminology that is broader in scope.