A Plea for Precision

This is an extended version of a presentation given at the Progress Educational Trust event at the 2015 Festival of Genomics, at which participants were asked, "Should we be using CRISPR-CAS9 to experiment on human embryos?

Introduction

There is no legal answer to the question, "*should we be using CRISPR-CAS9 to experiment on human embryos?*" The law permits CC9 experimentation on human embryos under an HFEA licence on the same basis as any other research application. CC9 is a common, well-established experimental tool and highly useful to any of permitted purposes under the *Human Fertilisation and Embryology Act*. However, the law has nothing to say about whether it should, other than its democratic mandate. My personal view is that of course we should permit use CC9 in this way, because research extends our knowledge of human development and our ability to deal with diseases and fertility problems. The question would be legally trite were it not for the possibility of that such research might lead to the use of CRISPR-CAS9 on human embryos intended for implantation. This is where a lawyer may indeed have something to say, not least by way of a plea for scientifically informed definitions and semantic precision.

Principle purposes

Let's just dispose of the main question by adding a little more detail. A successful application for a research purpose must satisfy the HFEA licensing committee that it has one or more of certain "*principle purposes*" listed by the *Human Fertilisation & Embryology Act*:

a) increasing knowledge about serious disease or other serious medical conditions;
b) developing treatments for serious disease or other serious medical conditions;
c) increasing knowledge about the causes of any congenital disease or congenital medical condition that does not fall within paragraph (a);
d) promoting advances in the treatment of infertility;
e) increasing knowledge about the causes of miscarriage;
f) developing more effective techniques of contraception;
g) developing methods for detecting the presence of gene, chromosome or mitochondrion abnormalities in embryos before implantation; or
h) increasing knowledge about the development of embryos.

CC9 and other genomic editing tools are (manifestly) valuable means of pursuing

these "*principle purposes*". But they are just tools: Kathy Niakan might just as well have applied to use a new sort of test tube. It would therefore be remarkable if the HFEA were to refuse Kathy Niakan's application. Nevertheless, subordinate purposes remain a concern to some. Most obviously, some are concerned that knowledge gained from research might lead to the genomic editing of embryos that are intended for implantation.

Currently, gene-editing embryos for implantation (or the gametes used to make them) is unlawful. However, the position could change with very minor amendments to the law. The *Human Fertilisation and Embryology Act 1990* was amended seven years' ago to provide a framework for mitochondrial donation under what are now the *Mitochondrial Donation Regulations 2015*, Article 7 of which permits two procedures (third party pronuclear transfer and maternal spindle transfer) for the purpose of preventing the transmission of serious mitochondrial disease. It would be straightforward to add a third, mitochondrial DNA editing, to article 7.

There's a huge (and under-appreciated) difference between mitochondrial DNA and mitochondrial genes. Only 13 proteins are coded by genes in mitochondria themselves (together with 24 genes for making them). The remaining 1,500 or so other mitochondrial genes are located in the nucleus. Why not edit them to prevent the transmission of mitochondrial disease, too? And if these, why not other nuclear genes to prevent the transmission of other serious heritable diseases? The answer, according to slippery-slopers, is that this would interfere with the human germ line and the human genome. They claim that this would contravene international law. I hope to convince you that genomic editing of heritable diseases would be lawful.

Genomic conventions: UNESCO & Oviedo

There is no international treaty on the human genome. However, opponents of embryonic gene editing commonly pray two international conventions from 1997 in support of what they claim is the illegality of human embryonic editing: the UNESCO *Declaration on the Human Genome* and the Council of Europe's "Oviedo" *Convention on Human Rights and Biomedicine*. The UK has subscribed to neither, so their restrictions are of no direct significance here. Nevertheless, factual and semantic analysis of the terms "*the human genome*" and "*the human germ line*" illustrates that these instruments do not necessarily forbid the editing of human inheritance, though they may in some instances.

"The human genome"

No human has ever been born with "*the human genome*". The culmination of the Human Genome Project was the sequencing of Craig Venter's genome, not everyone's. "*The human genome*" out-Venter's Venter: it's the library of all existing human genomes. Only a small fraction is exclusive to our species, and, unlike individual genomes, it transcends birth and death. Many who oppose human genome editing are apt to forget that human reproduction fundamentally disrupts existing genomes: taking two to create a unique, mortal hybrid. They may be reassured that "*the human genome*" is not compromised in any way by such sexual acrobatics.

Article 1 of the *UNESCO Declaration*, so frequently invoked by those seeking a blanket ban on genome editing, confirms that "*the human genome"* refers to the

set of all human genes in all conceivable genomes of humans who have been born[1]:

> *"The human genome underlies the fundamental unity of all members of the human family, as well as the recognition of their inherent dignity and diversity. In a symbolic sense, it is the heritage of humanity."*

Clearly, when the *UNESCO Declaration* refers to "*the human genome*", it is referring to humanity's enduring and evolving gene pool, not to individual, mortal genomes. The temporal scope of the provision is arguable: the reference to "*all members of the human family*" could be taken to include extinct human genes, for example Neanderthal or Denisovan genes that do not appear in any living human individual. On the other hand, the word "*heritage*" could be read as excluding genes which haven't survived into the present human population. It's up for debate, though unlikely to be of much practical significance.

The other instrument relied on by editing opponents is the *Oviedo Convention*, which is consistent with the *Declaration* in focusing on the integrity of the human gene pool and not on the genomes of individuals. Article 13 states:

> *"An intervention seeking to modify the human genome may only be undertaken for preventive, diagnostic or therapeutic purposes and only if its aim is not to introduce any modification in the genome of any descendants."*

We can readily tick off the purposes box (I doubt those looking for enhancement could get away with calling it "*prevention*", but who knows?). The forbidden "*aim*" would not be accepted under current law anyway. Taking the *Mitochondrial Donation Regulations 2015* as our benchmark, interventions are forbidden unless the HFEA determines that:

> • any embryo created by the fertilisation of an egg extracted from the ovaries of the particular woman named in the determination may have mitochondrial abnormalities caused by mitochondrial DNA; and
> • there is a significant risk that a person with those abnormalities will have or develop serious mitochondrial disease.

In other words, removing mutations from the gene pool is not a legitimate purpose: the only lawful aim under the *Regulations* is avoiding abnormalities in a future person. The HFEA will obviously take that to refer to the person born as a direct result. However, it would not in principle conflict with the Oviedo Convention if, besides that immediate and obvious aim, consideration were also given to the descendants of a person born following such an intervention. Using genome editing to secure the integrity of "*the human genome*" seems an entirely defensible position. Indeed, if Article 3 of the *UNESCO Declaration*[2] is interpreted as distinguishing "*the human genome*" from disease-causing mutations, it may even be obligatory, given prior knowledge of their existence, to correct them. In any event, such intentions (good or ill, depending on your perspective) are

[1] Under the 1948 UN Declaration on Human Rights, "dignity" arises at birth, although religious groups claim a wider meaning in support of their opposition to abortion.

[2] "*The human genome, which by its nature evolves, is subject to mutations*." (My emphasis.)

incidental to the lawful purpose of preventing disease in a person.

Again, the only rational reading of Article 13 is that, consistent with the UNESCO Declaration, it refers to the genome as an article of population genetics. The prohibition, such as it is, is against changing the human genome at the population level. It's intended to prevent the introduction of genes from outside the human gene pool and, perhaps, the re-arrangement of existing genes in a novel ways.

Indeed, not just genes: most of your DNA is non-coding, including a good deal of parasitical DNA: only 2% of "*the human genome*" actually consists of genes. In part, it's a forgivable lapse: when the *Declaration* and *Convention* appeared, it was estimated that "*the human genome*" included (in some people's minds, perhaps, "comprised") about 100,000 genes, a figure which was subsequently revised down to around 20,000 to 25,000. In any event, we now know a great deal more. It's therefore reasonable to assess coolly and rationally, in the light of the sequences involved, the science and any proposed interventions, whether it's reasonable or necessary to protect all the remaining 98% of our DNA. It may well be that it is, but it should not be assumed that the precautionary principle is always best.

The "*germ-line*"

The other much-discussed and foggily used expression is the human "*germ-line*". The embryological origins of germ cells are one thing, and it's possible to have an interesting discussion about how experiments in gametogenesis are breaking the historic barrier between somatic and germ cells, but it's not really getting to the central concern: the protection of an inviolable "*line*" of inheritance.

There seem to be two alternative meanings. At the individual-to-individual level, the only genes meaningfully to avoid the hurly burley of sexual reproduction to travel the generations together in an uninterrupted person-to-person "*line*" are the 37 maternally inherited mitochondrial genes. The alternative, more rational (and more human) meaning for the human "*germ-line*" is the totality of gene transmission within the entire human gene pool through all generations of all humans and their antecedents. This view is consistent with the potentially persuasive December 2015 statement of the International Summit on Human Gene Editing, which, under the heading, "*Clinical Use: Germline*", referred to:

> "*the obligation to consider implications for both the individual and the future generations who will carry the genetic alterations* [and] *the fact that, once introduced into the human population, genetic alterations would be difficult to remove and would not remain within any single community or country*".

Of more immediate relevance, it is consistent with the *Oviedo Convention*, the *UNESCO Declaration*.

Article 13 of the *Oviedo Convention* avoids the expression, "*the human germ-line*", but the accompanying explanations make clear that it is concerned with the inviolable "*line*" of inheritance:

> *"Interventions seeking to introduce any modification in the genome of any descendants are prohibited. Consequently, in particular genetic modifications of spermatozoa or ova for fertilisation are not allowed. Medical research aiming to introduce genetic modifications in spermatozoa or ova which are not for procreation is only permissible if carried out in vitro with the approval of the appropriate ethical or regulatory body."*

As the genome of an individual descendant doesn't exist before conception and cannot realistically be changed afterwards[3]3, it can hardly be "*modified*" by a past event. The only comparator for our descendant's genome is "*the human genome*" of today: if a proposed editing intervention would cause that person's genome to fall outside "*the human genome*" of today, then it is precluded by Article 13 (even though "*the human genome*" is evolving naturally anyway).

Notably, the explanations qualify the *Oviedo* prohibition on "*genetic modifications of spermatozoa or ova for fertilisation*" with the word, "*Consequently*". This confirms that the prohibition is concerned with the integrity of the human gene pool: if a proposed intervention would result in no change in the pool, Article 13 doesn't prohibit it. The *Oviedo Convention* certainly presents no cogent reason to ban interventions that do not change the human gene pool.

The *UNESCO Declaration* refers to germ-line intervention obliquely, in Article 24, when it mentions "*practices that could be contrary to human dignity, such as germ-line interventions*". Dignity is a right of individuals, arising on birth and expiring on death, not of populations. The only individual to be effected is thus a future person, as the word "*could*" suggests. "*Could*" also confirms that germ line interventions are not automatically contrary to human dignity. It might be contrary to a person's dignity if, for example, she were to be born with green fluorescent skin. On the other hand, she might be delighted, though her descendants might not be. An easier problem to resolve is knowingly allowing an embryo to develop despite the opportunity to correct a gene for Huntington's disease or cystic fibrosis. Deliberately creating such a person implies an intention to torture that would certainly be an affront to that person's dignity. Only the fact that there is no legal person at the time of the failure to intervene prevents the child from having a right of action, but this could change at the stroke of the legislative pen. Indeed, it might reasonably be suggested that such a failure to intervene should become a serious criminal offence.

In contrast to the *UNESCO Declaration* and *Oviedo Convention*, the UK is bound by the EU *Biotechnology Directive*[4]. The *Directive* is also consistent with the view that the human "*germ-line*" refers to the totality of gene transmission within the human gene pool. In the course of prohibiting patents for "*processes for modifying the germ line genetic identity of human beings*", it elegantly combines "*the germ line*" and "*the human genome*" in a formulation that clearly declares the mischief that the rule seeks to prohibit: modifications to the human gene pool. It provides a useful framework for assessing different genomic interventions

[3] For the sake of argument, we can ignore chimeras such as might be produced from somatic interventions in utero.

[4] Recital 40 & Article 6 Directive 98/44.

(beyond the field of patents), inviting us to distinguish between those interventions that would change the "*germ line genetic identity of human beings*" and those that would not.

On this basis, human-to-human mitochondrial transfer won't, for all the media excitement, change the "*germ line genetic identity of human beings*" one jot. Nor would replacement of a genetic mutation with a recognised "working" sequence from another human. However, some interventions are less certain. For example, would a deletion change the gene pool? Probably not, but we need to consider such things carefully. A mere sequence change might alter the "*germ line genetic identity of human beings"*, but not necessarily. Other interventions certainly would modify the genetic inheritance of our species, and we need to assess each of these, coolly and rationally in the light of experimental evidence before deciding what the law should be.

It's striking that, even though (like the *UNESCO Declaration* and *Oviedo Convention*) the *Directive* was formulated in the heat of the Human Genome Project, it uses the expression "*genetic identity*" instead of "*the human genome*". But what does the *Biotechnology Directive* mean by "*genetic identity*"? Does "*genetic*" only refer to the 2% of the genome that contains genes? Today, we have reason to be less cavalier about "junk" DNA, but it is at least a claim to exclude non-functional DNA from our cares. In practice, it won't matter: who would bother to edit something non-functional?

What about the word, *"identity*"? Because identical proteins can be encoded by different DNA sequences, it's strongly arguable that *"identity*" concerns the expression of proteins, rather than the identity of the code itself. For example, because the amino acid lysine may be coded AAA or AAG, variants coding for the exactly same protein inevitably occur within the human population. As "*the human genome, which by its nature evolves, is subject to mutations*[5]" and as the full script of "*the human genome*" is unknowable for practical purposes[6], we can never say that a lysine encoded AAA at a site where AAG normally appears is not within "*the human genome*". Of course, proteins are coded by immense strings of codons, so over the course of time, natural selection's indifference to AAG and AAA has lead to the same protein being coded by different codon sequences in different individuals, with even greater differences between different species. Codon strings may also be interrupted by introns, which also vary as species become further apart, but these are also irrelevant, because they are excised during the standard eukaryote transcription process, the end result of which is exactly the same protein: the thing that natural selection does care about. It's only at this level that genetic "*identity*" has any real meaning. When a protein is identical (and the clue is in the word), it's as preposterous to speak of porcine or Eskimo versions as to assert that Fords are made of Ford iron while Mercedes are made from Mercedes iron.

Of course, this is just too rational for those who identify DNA with the things that

[5] Article 3, UNESCO Declaration.

[6] Because no-one will ever sequence the genome of everybody on the planet.

they encode: people who imagine that deoxyribonucleic acid comes in human and animal DNA flavours. They include those MPs and members of the House of Lords who in 2008 crayoned "*animal DNA*" into the *Human Fertilisation and Embryology Act 1990*. In considering genome editing, we need legislators and policy makers to move beyond this level of scientific witlessness. DNA found in cattle is not intrinsically "bovine", nor that in dogs "canine": it's just DNA. Of course, particular sequences may only be found in cows or spaniels, but there again, they may not and, if the end product is identical with that from another sequence, natural selection doesn't care and nor should we. Indeed, the more fundamental particular genes are, the more likely they are to be functionally or literally interchangeable. Use a cardinal's Hox gene to recreate the normal human sequence in an embryo that would otherwise develop abnormally, and (assuming cardinals to be human) "*the human genome*" won't change a whit. However, the same may also be true if, instead of a cardinal, you get your Hox genes from a fly. Indeed, the sole instance of individual-to-individual "*human germ-line*" transmission, the 37 genes found in mitochondrial DNA, is just as fundamental to most other creatures too.

In its statement of December 2015, the International Summit on Human Gene Editing observed that:

> *"many nations have legislative or regulatory bans on germline modification. However, as scientific knowledge advances and societal views evolve, the clinical use of germline editing should be revisited on a regular basis."*

Indeed. However, ethical debate is meaningless unless participants adopt a common language with shared, scientifically-informed, dispassionate meanings to key terms.