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Martin, P.A. and Turkmendag, I. (2021) Thinking the unthinkable: how did human germline genome editing become ethically acceptable? New Genetics and Society, 40 (4). pp. 384-405. ISSN 1463-6778

https://doi.org/10.1080/14699915.2021.1932451

Thinking the unthinkable: How did human germline genome editing become ethically acceptable?

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Abstract

Two major reports in the UK and USA have recently sanctioned as ethically acceptable genome editing of future generations for the treatment of serious rare inherited conditions. This marks an important turning point in the application of recombinant DNA techniques to humans. The central question this paper addresses is how did it became possible for human genetic engineering (HGE) of future generations to move from an illegitimate idea associated with eugenics in the 1980s to a concrete proposal sanctioned by scientists and bioethicists in 2020? The paper uses the concept of a regime of normativity to understand the co-evolution and mutual shaping of technology, imaginaries, norms and governance processes in debates about HGE in the USA and UK. It will be argued that interlinked discursive, institutional, political and technological changes have made proposals for the use of genome editing in the genetic engineering of future generations both 'thinkable' and legitimate.

Keywords: Genome editing; gene therapy; IVF; ethics; eugenics

1. Introduction

Two major policy reports in the UK and USA have recently sanctioned as ethically acceptable the use of human genetic engineering (HGE) to alter future generations– so called germline therapy – for the treatment of serious rare inherited conditions (National Academy of Sciences, 2017; Nuffield Council on Bioethics, 2018). This marks an important turning point in the application of recombinant DNA (rDNA) techniques on human. The history and development of molecular genetics has been haunted by the spectre of eugenics and fears that HGE would lead down the slippery slope to genetic enhancement. Throughout the 1970s and '80s the use of rDNA on humans was highly controversial and just 20 years ago the application of this technology to future generations was outlawed in many jurisdictions and by international organisations such as UNESCO. The central question this paper addresses is how did it became possible for HGE of future generations to move from an illegitimate potential application of rDNA associated with eugenics to a concrete proposal ethically sanctioned by scientists and bioethicists in 2020?

One answer to this is the arrival of a powerful new technology – genome editing using CRISPR cas9 – that has revolutionised the ability to manipulate DNA. However, this paper will argue that the

advent of a better technology is only part of the reason why HGE has become "thinkable". A more complete understanding requires a detailed exploration of the long-running debate on this topic going back to the 1980s. It will be shown that a series of discursive, institutional, political and technological changes have enabled this transition. In analysing these changes, the concept of a 'regime of normativity' will be elaborated to understand the co-evolution and mutual shaping of technology, future imaginaries, norms and governance processes in debates about HGE in the USA and UK. A regime of normativity is composed of the ethical principles, expectations, informal rules, routine practices and formal regulations that guide the actions of scientists and innovators in relation to a specific domain of knowledge production.

A comparative approach is taken to highlight both differences and similarities in the evolution of the regime of normativity associated with the two key technologies underpinning HGE – gene therapy and in vitro fertilisation (IVF). The USA led the world in the development of gene therapy in the 1990s and 2000s, but more recent proposals for the application of genome editing to reproductive tissues have been mired in controversy. In contrast, the UK has led the world in the development and regulation of IVF and recent proposals for the genome editing of embryos have found support amongst both professionals and patient groups. This has created the conditions that have allowed the first tentative proposals for human germline genome editing to be outlined. They have still to be sanctioned by regulatory bodies, but this paper will conclude that a fundamental shift in the framing of HGE has occurred that now makes this ethically acceptable.

2. Conceptual framework

The notion of a 'regime of normativity' is a valuable conceptual tool for understanding how the work of scientists and innovators is guided by a negotiated set of principles, norms and processes. The broader concept of a regime as it relates to forms of governance has multiple meanings reflecting different disciplinary traditions. It was first developed within International Relations to understand the emergence of rule-based co-operation in the international system. In this context, a regime is seen as distinct from an institution and can be defined as: "Implicit or explicit principles, norms, rules, and decision-making procedures around which actors' expectations converge in a given area of international relations." (Hasenclever, Mayer and Rittberger, 1996). These shared norms and processes provide the foundation for negotiation and coordination between (state) actors.

More recently the idea of a "socio-technical regime" has been developed by Geels and other scholars within STS and innovation studies to understand stability and change in different technological

systems. This emphasises the co-production of knowledge, rules, and institutions as new technologies are developed and adopted into practice. Here the idea of a socio-technical regime is seen as forming the 'deep structure' that orient and coordinate the activities of the social groups that create and reproduce the various elements of socio-technical systems (Geels, 2011). These might include innovators, producers, regulators and consumers. Within this framework a regime is composed of institutionalised formal and informal rules (e.g. shared beliefs and values, routines, regulations, practices) that mutually construct and are constructed by actors within a socio-technical system. There is an extensive literature looking at socio-technical regime transitions in the context of debates about the management of sustainable energy, transport and economic development (Geels, 2018). For example, the shift from hydrocarbon-based energy systems to ones using renewables involves the creation of new norms and governance processes, as well as technological infrastructures. However, there have been few detailed case studies exploring exactly how the principles, norms and rules that form a core element of socio-technical regime are negotiated between actors.

This paper is concerned with the ethical governance of an emerging biotechnology and will draw on Pickersgill's conception of 'regimes of normativity' (Pickersgill, 2012). Whilst this does not adopt the framework developed by Geels et al, there are similarities with an emphasis on the co-production of knowledge and norms. In this case, a regime of normativity refers to "an analysis of the association between scientific work … and the webs of official and informal institutions, agents and discourses that prescribe what scientists ought to do." (Pickersgill, 2012). This concept seeks to locate normative discourses in a much wider context than formal regulatory bodies and arguments within moral philosophy. Such a regime might include formal ethical principles and review, informal moral discourse, and official/unofficial protocols within specific scientific communities. Science and ethics are not two separate domains but are deeply entwined, with the work of scientists creating new ethical issues and the response to these feeding back to influence what researchers can or cannot do (p597).

A particular regime of normativity may therefore shape knowledge production through the creation of new kinds of symbolic and material ''resistances''. In this way, ethics becomes embedded within the very fabric of laboratory life with scientists incorporating normative reflection into their daily practices (p598).

This paper seeks to further elaborate this concept beyond the laboratory to include the development of new technologies, clinical practices, the design of artefacts and the development of commercial products. In this context, a regime of normativity constitutes a distinctive core element of the broader socio-technical regime surrounding a technology and is articulated through professional codes of practice, regulatory institutions, legislation, as well as the everyday work of innovators. By analysing the temporal emergence of a regime of normativity it becomes possible to understand the dynamic processes of social negotiation between groups, the power and influence of different actors and the

broader cultural influences that shape the principles and norms governing a new technology. This framework provides a valuable understanding of how these in turn influence the broader development of the technology at the macro level.

A key element in the construction of techno-scientific regimes of normativity are shared expectations for the future applications of new knowledge. These are important in creating moral-technical imaginaries. In a study of internet convergence in an American television network Fish (2015, p1) describes:

> "How emergent technologies are imagined, discussed, and implemented reveals social morality about how society, politics, and economics should be organized. … The simultaneity of technical, moral, and social ordering defines the "moral technical imaginary." (Fish, 2015)

This notion draws on work in STS on socio-technical imaginaries (Jassanoff and Kim, 2015). In thinking about the future, it therefore becomes important to think about the ethical governance of emerging technologies and what limits might be placed on them.

Another key insight is that such future making activities are a collective process that take place in 'communities of promise' (Martin, Brown and Kraft, 2008) composed of scientists, innovators, users, policymakers and other stakeholders. The ability to build a powerful community of promise around an emerging technology can be crucial in its success or failure.

Other authors (Thompson 2005; Franklin 2013) have addressed the co-production of ethics, norms, technology and governance frameworks by taking a more ethnographic approach. Thompson introduced the term 'ontological choreography' to describe "the dynamic coordination of the technical, scientific, kinship, gender, emotional, legal, political, and financial aspects of ART clinics" (p8). In a similar vein, Franklin has analysed the normalisation of reproductive technologies and identifies IVF as a technological platform that de-naturalised biology while remaining "embedded in naturalized and normalized logics of kinship, parenthood and reproduction"(p.4). These studies provide important insights and background to this study.

This paper will therefore examine the origins and development of the regime of normativity that is emerging around genome editing. It will describe the history of research in two key areas – gene therapy and IVF. It will trace how ethical issues have been problematised, the normative principles that have been developed to enable research to proceed, the institutionalisation of these norms and how these have shaped the work of scientists, clinicians and companies. It will also outline the shared moral-technical imaginary that has guided these fields. This is a wider interpretation of the concept of a regime of normativity than that offered by Pickersgill and is closer to that of Geels in going beyond

the laboratory, but retains the focus on ethical debates, formal and informal regulation and the shaping of techno-scientific work.

3. Data sources and methodology

The analysis presented here builds on the longstanding engagement of the individual authors with the history and contemporary development of gene therapy (References to Author 1) and IVF and other reproductive technologies (References to Author 2). In particular, it draws on previously unpublished research on the early development of gene therapy in the USA (Author reference) and detailed analysis of key legal and policy reports, public consultation documents and parliamentary records. The main documents were chosen after bibliometric analysis of PubMed and Web of Science using a range of search terms including "human genetic engineering", "gene therapy", "genome editing" to identify scientific, clinical and bioethical papers discussing HGE from 1980-2020. A comprehensive search of government publication databases and careful tracing of the debate on HGE within the UK Parliament (via Hansard) and in the USA through the work of leading science policy institutions was also undertaken. Key documents included: three reports published by the Nuffield Council on Bioethics: Novel techniques for the prevention of mitochondrial DNA disorders: an ethical review (2012), Genome editing: an ethical review (2016), and Genome editing and human reproduction: social and ethical issues (2018), reports by the US National Academy of Sciences and National Academy of Medicine: Mitochondrial Replacement Techniques Ethical, Social, and Policy Considerations (2016) and Human Genome Editing: Science, Ethics, and Governance (2017), and British parliament records of the two debates held on held on 31st of October 1984 and 5th of December 2002 (Human Fertilisation: Warnock Report and Stem Cell Research: Select Committee Report, respectively). Our aim was threefold: describing and critically evaluating the content of these documents, understand the structure of the changing discourse and debates, and uncovering hidden themes. This was supplemented by searches of relevant legal texts and legislation. The analysis took as its starting point a rereading of previous work in this area (Evans, 2002), (Mulkay, 1997) and was followed by primary analysis of the key documents to identify the main elements in the regime of normativity emerging in the two technological domains. Each author led on analysing one domain with ongoing comparison between the two to ensure consistency and robustness of findings.

4. The first debates on human genetic modification: forming the Gene Therapy regime of normativity

The idea of human genetic modification has a long history. Its origins were heavily influenced by eugenics in the pre-war era, and reform eugenic ideas continued to shape the thinking of the pioneers of post-war molecular genetics (e.g. Crick, Sinsheimer) up until the 1970s. With the advent of recombinant DNA (rDNA) societal concerns took root around fears about the containment of genetically modified bacteria and came to a head in the wake of the first attempt to apply rDNA to humans. In 1980 a leading US clinical researcher, Martin Cline, tried to correct the genetic defect causing thalassaemia in two children in Israel despite being refused permission from his local Institutional Review Board in the USA (Beutler, 2001). This caused an international outcry and sanctions against him. One of the main responses to the Cline controversy was a major inquiry by the Presidential Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research (President's Commission) on the 'ethics of genetic engineering with human beings' which produced the landmark report *Splicing Life* in 1982 (President's Commission, 1982). This proved to be the most important analysis of the subject for the next 20 years and provided the foundational framework for all subsequent discussions of HGE (Evans, 2002).

The report considered the technical and ethical issues surrounding what it called "zygote therapy" – the combination of gene transfer with IVF to alter germ cells to cure inherited disease. It suggested that this could have the advantage of ensuring the person treated and their offspring would be free of the disease and also "reduce the overall frequency in the population of genes that usually have deleterious consequences" (p46). However, the report went onto say that although the technique may hold "great promise" it was fraught with technical risks and uncertainties, as well as serious ethical issues. Specifically, it highlighted strong concerns that altering the human gene pool by eliminating "bad" genes is a form of eugenics (p47). It concluded that there were "strong contraindications against therapy of fertilized eggs or embryos becoming a useful clinical option in the near future." (p48). It did, however, distinguish between such germline application and so-called somatic therapy involving non-reproductive cells; the latter being seen as ethically acceptable.

In making this judgement the Commission started by stating that it *"*…found no ethical precepts that would preclude the initial clinical uses of gene splicing now being undertaken or planned" but recognised that more distant possibilities might have less benign effects. The issue it spent most time discussing was the mainly religious objection that applying gene splicing technology to alter future generations was Playing God.

Having debunked the religious objections, the report went on to consider concerns about the potential consequences of the technology, including possible likely outcomes, such as adverse events, psychological harm, stigma, and the evolutionary impact on human beings. This highlighted the way in which zygote (germline) therapy might alter parental rights and responsibilities: "… It seems safe

to say that one important duty of a parent is to prevent or ameliorate serious defects (if it can be done safely)" (p65) . However, it should be noted that the focus of this discussion was mainly on the duty of parents to prevent the suffering of their child rather than their *right* to have access to the technology or to have a healthy child. In addition, the report noted that if genetic engineering could reduce the burden of disease on their victims and society then "mandatory genetic treatments may be advocated" in the future (p66). Here again the discourse is concerned with fear of coercion rather than rights.

In summary, *Splicing Life* laid the foundation for the regime of normativity associated with gene therapy. It achieved this by framing the normative debate in terms of the safety and uncertainty surrounding HGE technology and its potential social and ethical consequences. The latter were to be addressed in terms of the principles established by the new profession of bioethics. It raised no fundamental ethical objection to the development of HGE arguing only that it was premature. The discursive separation of somatic from germline applications allowed scientific research on somatic gene therapy to proceed.

The consolidation of somatic gene therapy in the early 1990s

Following the work of the President's Commission, the first proposals for the clinical development of somatic gene therapy were made in the mid-1980s. In response, the National Institutes of Health (NIH) mandated the Recombinant Advisory Committee (RAC), which had been initially created to govern the safety of rDNA technology, to establish a regulatory framework for somatic gene therapy. The Human Gene Therapy Sub-committee (HGTS) of the RAC was tasked to do this and they adopted the Belmont principles and drew up six criteria by which to evaluate human gene therapy proposals. These were then used to develop detailed clinical guidelines on informed consent, the assessment of risks and benefits, and the selection of participants (NIH Recombinant Advisory Committee, 1986). In this way, the normative foundation of the regime of normativity established by the President's Commission became embedded in scientific and clinical practices, and the design of technology, treating the application of rDNA to somatic cells as no different from other medical therapies. Although the Sub-Committee placed a moratorium on germline alteration, it adopted an explicit policy of not ruling out germline applications in the future (Nichols, 1988).

Despite keeping the door open to germline alteration, the discursive separation of somatic from germline modification served an important legitimating function and the RAC guidelines laid the foundation for the expansion of research on somatic therapy and eventually the approval of the first gene therapy clinical trial in 1990. Key to this was the elaboration of a moral-technical imaginary first outlined in *Splicing Life* in which somatic gene therapy was constructed as an important treatment for a range of important diseases, most notably cancer, as well as rare genetic disorders (Martin, 1999).

Following this landmark event, the field grew rapidly with over 160 clinical trials in the USA and 90 internationally within six years. The governance regime established by the RAC was adopted by many other countries in the next decade and acted as the *de facto* Gold Standard for the regulation of somatic gene therapy internationally (Cohen-Haguenauer *et al.*, 2002).

The development of gene therapy in the UK lagged well behind the USA, with the ethical issues surrounding the technology only being officially considered by the report of the Clothier Committee in 1992 (Clothier, 1992). It drew very similar conclusions to *Splicing Life* and there was limited debate on HGE. However, it also kept the door open to germline intervention arguing that it should not yet be attempted as: "… there is at present insufficient knowledge to evaluate the risks to future generations." (Para 5.1)

Attempting to reopen the debate on germline modification

The years immediately after the first clinical trials were a time of great hope for the technology and several of the pioneers of gene therapy returned to debating the ethics of germline modification with the aim of liberalising policy to enable its clinical development. This followed a call by the Chair of the HGTS, LeRoy Walters, for a public discussion of the ethical issues surrounding germline genetic intervention in humans (Walters, 1991). These discussions were published in a series of papers in leading scientific and bioethical journals that increasingly drew on a new distinction between therapy and enhancement (Zimmerman, 1991).

This distinction had first been made by the leading scientific advocate of gene therapy, W. French Anderson, in an influential article published in 1985 (Anderson, 1985). In this he differentiated between three types of genetic engineering of future generations; a) germline 'therapy' for the treatment of genetic disease; b) enhancement of simple characteristics, such as height, and c) eugenics to 'improve' complex human traits. For Anderson, germline therapy was ethically acceptable whereas enhancement and eugenics were not. This move to provide a medical rationale for germline engineering and its separation from enhancement was subsequently widely adopted in the bioethics literature (President's Council, 2003). Reflecting on the criteria drawn up by the HGTS to evaluate somatic gene therapy a leading bioethicist observed that "… they will ultimately lead us to approach the moral limits of gene therapy as a professional policy question about the goals of medicine, rather than as a social policy question about the public good." (Juengst, 1990)

This placed the governance of germline therapy firmly in the medical domain and under professional control, rather than allowing it to be a question for open public debate and politicisation. However, this also raised other questions about the role and limits of medical authority. One answer to this issue that gained increasing traction in the bioethical debates of the mid-1990s was that germline

modification should be seen as a reproductive technology subject to the control of potential parents exercising their right to autonomy and reproductive health (Evans, 2002).

Despite the growth of professional support for developing germline gene therapy as a medical technology to treat genetic disease in future offspring, there was limited support for this outside biomedicine. The formation of a coherent community of promise was further limited by resistance from powerful groups opposed to embryo research. No meaningful progress was made in taking this forward practically as the RAC moratorium remained in place. By the late 1990s the discussion of germline therapy had largely been overshadowed as investment in somatic gene therapy grew rapidly with an increasing number of firms involved in commercialising the technology. However, this growth came to an abrupt end following the death of Jesse Gelsinger, a patient receiving an experimental therapy, in 1999 and the subsequent deaths of several French children receiving gene therapy for SCID in 2002.

The lost years and the return of hope for somatic gene therapy

In the next decade the clinical development of somatic gene therapy proceeded slowly with falling commercial investment and a series of further disappointments. However, by 2010 a review of the field could claim that after two decades "success is finally mounting" following positive results from trials for ocular diseases and inherited immune deficiencies. The first commercial gene therapy product (Glybera) was approved in the EU in 2012 and in the USA (Spinraza) in 2016 (Shahryari *et al.*, 2019). By 2020 there were starting to be several commercially successful products on the market for rare genetic disorders, massive private investment in the field and several hundred companies developing the technology. This helped consolidate the moral-technical imaginary around somatic gene therapy as a treatment for rare inherited disorders.

The growing use of gene therapy in treating disease and the successful commercialisation of these products provided both clinical validation, and helped stabilise the sociotechnical system that had been assembled around it over 40 years. A central element of this was the construction of a regime of normativity associated with somatic gene therapy, first outlined in Splicing Life and later institutionalised by the RAC and the FDA. This provided the guiding principles shaping both the design and use of the technology and the work of innovators and clinicians. This regime was controlled by the scientific and clinical professions, and depended on the separation of somatic from germline applications, the adoption of bioethical principles with a focus on safety, risk and equity, and the normalisation of gene therapy as being no different from other biological drugs. One important consequence of this was the marginalisation of any significant discussion of germline gene therapy between 2000-2020.

5. The constitution of the In Vitro Fertilisation (IVF) regime of normativity

The world's first test-tube baby, LouisE Brown, was born in the UK in 1978 using the new technique of in vitro fertilisation (IVF). In response, the UK government established a committee of inquiry into the social impacts of infertility treatment and embryological research in July 1982. Mary Warnock was asked to chair the inquiry. Much of the discussion of the Committee focused on the ethics of different reproductive techniques, such as artificial insemination, gamete donation, embryo freezing, surrogacy and IVF, and how these should be governed. The main issues relating to research were the legal status of the human embryo, how it should be protected and safeguarding the public interest.

The Warnock Report was published in July 1984 (Warnock, 1984) recommending that embryo research should be allowed to continue if limited to a 14-day timescale. The Committee also proposed that embryo research should be regulated, licensed and restricted in scope, as well as monitored and controlled by a body outside the research community. These principles laid the foundation for the regime of normativity associated with IVF.

In the section of the Report on the "Prevention of genetic defects" the Committee noted that it may in future become possible to insert a replacement gene to remedy such defects. It went on to acknowledge that public fears concerning this centred on "overtones of selective breeding" but regarded such techniques as purely speculative and precluded by the proposed regulations (p74). However, the door was left open to genetic modification of embryos in the future as the Report envisaged that its guidance would be reviewed from time to time to take account of changes in scientific knowledge and/ or public attitudes.

The recommendations of the Committee proved highly controversial and were initially opposed by the scientific community because of the restrictions placed on their research activities. They were also bitterly resisted by various religious groups and the proposals were debated extensively in both chambers of the UK Parliament between 1984 and 1990. Constructing a science-based distinction between the pre-embryonic and embryonic stage via the 14-day rule was crucial in winning Parliamentary support. Furthermore, the advocates of IVF also created a powerful "rhetoric of hope" (Mulkay, 1997) that framed these new technologies as helping childless couples to have a baby, but also to have a healthy child free from disease and disability. This was reinforced by the pro-research lobby mobilising patients and their stories to justify embryo research. Here a community of promise was created that went beyond the professional domain based on a moral-technical imaginary that closely linked advances in reproductive research to the cure of genetic disease.

After a long public debate, the recommendations of the Warnock Committee were accepted, embedded in legislation (the 1990 HFE Act) and institutionalised in the establishment of the Human Fertilisation and Embryology Authority (HFEA), the world's first fertility treatment and embryo research regulator. The principles set out by the Warnock Committee were subsequently widely adopted in many countries, in effect establishing the UK as setting the Gold Standard in this field (Matthews and Gallego Marquez, 2019). It should be noted that the key role of the HFEA in both regulating IVF as a medical technology and governing embryo research served to blur the boundary between research and the clinical application of IVF, ensuring these were closely linked in the public imagination.

The robust governance regime centred on the HFEA created a stable niche within which embryo research and the wider development of IVF as a clinical practice could proceed. The use of the technique was popularised by dedicated clinics with private provision playing a key role, and the number of treatment cycles in the UK increased from a few thousand in 1991 to over 60,000 in 2017 (HFEA, 2017). By 2018 it was estimated that in the 40 years since Louise Brown over 8 million babies were born worldwide as a result of IVF (Scutti, 2018). The massive expansion and success of IVF provided clinical and market validation, normalising and entrenching the sociotechnical system associated with its use. A key component of this was the construction of the regime of normativity associated with both IVF and embryo research as established by the Warnock Report and institutionalised in the creation of the HFEA. This provided the guiding principles shaping both the clinical use of IVF and the work of scientists and clinicians in refining the technique and extending its reach. At the creation of this regime there was no sanctioning of the development of germline genetic modification of embryos, but over the next few decades this normative and institutional framework would develop to make this possible.

6. Human cloning and the Stem Cell Research Debate

Almost twenty years after the first test tube baby, the creation of the cloned sheep Dolly in 1997 led to new debates over issues that the 1990 HFE Act had not envisaged. At the time there was a high level of public and professional concern over the potential misuse of cloning to create genetically identical copies of people. In response, the UK Government commissioned a consultation paper by the HFEA and the Human Genetics Advisory Commission in 1998. This supported a distinction between so called "reproductive cloning", which might lead to the birth of a child, and "therapeutic cloning" which does not alter future generations. In order to enable the latter, the report proposed amendments to the existing 1990 HFE Act to allow "developing methods of therapy for mitochondrial diseases and developing methods of therapy for diseased or damaged tissue or organs" (O'Neil and Deetch, 1998).

These amendments were discussed in Parliament - the so called stem cell research (SCR) debate – which took place between 1999-2001. While opponents of SCR continued to stress the embryo's fundamental moral status from conception, the pro-research lobby drew upon the science-based discourse which positioned the 14-day rule as addressing this concern (Parry, 2003) By mobilising patient support groups, advocates of SCR also successfully constructed a demand for curing disease and disability using stem cells, which successfully undermined opposition. Here again the moral-technical imaginary linking biological research and the treatment of incurable genetic disease played a key performative role.

In 1999 the Government established a committee led by the Chief Medical Officer, Professor Liam Donaldson to consider the suggested amendments to the HFE Act that would allow (embryonic) stem cell research to develop therapeutic uses of cloning techniques. The Government eventually accepted the Donaldson Report recommendation (Department of Health, 2000) that therapeutic cloning be allowed, but that the ban on human reproductive cloning be reinforced. Following this, the Human Reproductive Cloning Act 2001 outlawed this possibility and new regulations set out strict conditions under which the HFEA could grant licences for therapeutic cloning research. It is notable that the Donaldson report made no direct reference to germline genetic modification, despite the development of human embryonic stem cells making this technically easier.

Around the same time as the SCR debate there was also public controversy about the development and potential use of preimplantation genetic diagnosis (PGD), where the genetic status of an embryo is assessed to allow selective implantation during IVF. This was developed to enable couples with a family history of genetic disease to have a healthy child but could in principle also be applied to select for other genetic and chromosomal characteristics (e.g. sex). In 1999 the HFEA launched a consultation on this and the discussion of PGD in public and media discourses became increasingly couched in terms of the idea of "designer babies", a negative trope that would later frame criticism of genome editing in the UK and the US (Nerlich, 2019). The HFEA agreed that the technique could be used as a way of couples having a healthy child, but this was only finally allowed in the UK in 2003. A detailed analysis of the evolution of the regime of normativity associated with pre-natal testing is beyond the scopes of this paper, but its links to eugenic practices should be highlighted (see Mahowald 2006). The idea of a designer baby sits at the interface between the negative genetic screening of undesirable traits and the elimination of the same characteristics via genetic engineering. It should also be noted that the discourse of patient choice has been central to justifying its use and overcoming concerns about eugenics and enhancement.

The debates on stem cells and PGD further expanded the regime of normativity associated with IVF. Whilst drawing on the same framing, with IVF seen as a treatment for infertility, this marked the start

of an important shift, forging an increasingly strong link between reproductive technology and the treatment of genetic disorders.

7. Moving toward germline modification: Mitochondrial replacement techniques

By the early 2000s and in the wake of the cloning controversy, bioethicists, policy makers, scientists and many governments were increasingly drawing a red line between somatic genetic modification and germline modification. Almost 40 countries prohibited germline modification due to the fear of potential irreversible harms to the next generations and opening the door to market-based eugenics. This stance was underpinned by a series of international legal instruments (Council of Europe, 1997; UNESCO, 1997).

This moratorium started to come under pressure following success in developing the new technique of mitochondria replacement therapy (MRT) to avoid inherited mitochondrial disease. The HFEA ran a consultation on this and advised Government to permit MRT in the UK (HFEA, 2013). The Nuffield Council on Bioethics (NCoB), a key quasi-official body, also recommended that MRT would be an ethical treatment option (NCoB, 2012). The responses to a Department of Health consultation were also "generally positive" (Department of Health, 2014).

This broad agreement was highly significant, as MRT involves modification of the mitochondrial DNA in a way that the change will be passed to future generations. However, the UK Government concluded that compared to nuclear DNA, making changes to mitochondrial DNA was relatively insignificant in one's genetic make-up. With the passage of the Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015, the UK became the first country to allow germline genetic modification. It is worth noting that none of the international instruments mentioned above that prohibit germline modification are legally binding in the UK.

As with the introduction of IVF and stem cell research there was both formal consultation and considerable public discussion of the issues surrounding MRT. During the debate held in the House of Commons in September 2014, opponents of MRT argued that the techniques were unsafe and unpredictable. Drawing on a slippery slope argument they also expressed concern that the techniques would lead to human genetic modification, designer babies, and eugenics. In contrast, advocates framed it as an IVF technique for the 'treatment', 'therapy' or 'cure' that would alleviate the suffering of families that were affected by this rare genetic disease (Turkmendag, 2018). This further expanded the moral-technical imaginary linking IVF and genetic research.

Significantly, during the MRT debate and consultation a new line of argument was deployed to legitimise the use of the technology. This centred on the 'right-to-have a healthy child' and suggested that the use of reproductive technologies is an integral part of reproductive rights. Publicity was given to one patient's story – Sharon Bernardi - who had lost eight children due to mitochondrial disease. In the media coverage of MRT, treatment became blurred with a right to treatment, with Bernardi claiming: 'It is everyone's *right* to have a healthy child' (Turkmendag *et al.*, 2019).

Even though there is no legal recognition of the 'right-to-have a healthy child', the European Convention of Human Rights protects the 'Right to respect for private and family life'. Article 8 and case law have been interpreted by the European Court of Human Rights as being in the sphere of protection of Article 8, and this right could similarly extend to mitochondrial donation (Niekerk, 2017). The emphasis on the rights of prospective parents to access NRTs enables the further enrolment of this group into the community of promise surrounding IVF. The growth of this rights discourse is tied closely to the rise of patients as "consumers" since the 1970s, with patient groups coalescing around the notion of patients 'rights' (Mold, 2010).

Following the UK's debate on MRT, the US Institute of Medicine (IoM) established an expert committee to consider whether the clinical application of MRT was permissible. In February 2016 the committee published a report which drew similar conclusions to those of the NCoB (NCoB, 2016). The perceived importance of having a genetically related healthy baby was also emphasised by IoM, with it concluding that the use of MRT to enable parents to have a genetically related healthy child is justifiable (National Academy of Sciences, 2016).

The first child to be born using MRT was in 2016. However, the scientists behind this case divided the execution of the whole procedure between the USA and Mexico in order to avoid US legal restrictions on MRT (Palacios-González and Medina-Arellano, 2017). It should be noted that as of October 2020 no child has been born in the UK using MRT.

The development of MRT marked a decisive shift in the regime of normativity associated with IVF, with the technology increasingly framed in terms of the treatment of genetic disease and the emergence of a powerful discourse promoting a new set of normative principles; the rights of parents to have a genetically related healthy child. The MRT debate was also important in establishing a precedent allowing germline modification, even if this was largely rhetorical.

8. Moves towards human genetic modification

The debate on genome editing in the USA

The discovery of CRISPR cas9, a powerful new genome editing (GEd) technique in 2012, heralded a major advance in making fast, cheap and accurate changes to DNA and prompted concern about its social and ethical implications. In 2015 a group of leading scientists and ethicists called for the community to explore the challenges raised by human GEd and provide guidance on its acceptable use (Baltimore *et al.*, 2015).

In the USA the National Academy of Science (NAS) and the National Academy of Medicine (NAM) set-up a joint initiative to explore the implications of GEd and facilitate domestic and international dialogue. Its first activity was an International Summit on Human Gene Editing. It then established a Committee on the scientific, medical, and ethical aspects of genome editing which produced a major report in 2017 (National Academies of Sciences, 2017).

In its analysis the report clearly places the governance of GEd within the same regime of normativity as described above for gene therapy (p29). It contrasted this with the "alternative governance regime" in the UK which "…has more centralized and intensive regulatory control over therapies that involve gametes and embryos." (p58).

A significant part of the report dealt with the issues raised by germline modification (Chapter 5), highlighting the desire of parents to have a healthy and genetically related child. It also constructed the treatment of rare genetic diseases as a sizeable public health problem, which could be alleviated by heritable GEd for some families (p111). This was immediately followed by discussion of MRT. The narrative therefore frames the debate in terms of the desires of parents, the possible use of GEd to solve a major health problem and the precedent established by MRT. However, the Committee acknowledged that considerable technical difficulties remain to be overcome before GEd of early embryos is possible (p116).

In considering how to balance individual benefits and societal risks the report emphasised the right of individuals and the need to justify any restrictions on (reproductive) liberty. A series of potential risks are identified, notably the spectre of eugenics and the threat to disability rights, as well as the slippery slope in which germline editing will inevitably lead to genetic enhancement. The latter is extensively discussed in a separate chapter with more space devoted to it than any other ethical issue.

NAS concludes: "In some situations, heritable genome editing would provide the only or the most acceptable option for parents who desire to have genetically related children while minimizing the risk of serious disease or disability in a prospective child" (p133). This echoes the new discourse established during the MRT debate and marks an important shift in the regime of normativity associated with gene therapy.

The Recommendations chart a careful way through the complex US regulatory system and propose a series of criteria for clinical trials, noting that such trials could only proceed with broad public support. Despite this generally positive assessment made by the NAS, considerable barriers remain to the further development of germline GEd in the USA. In 2015 the NIH said it would not fund GEd research on embryos and in 2019 Congress passed legislation to ensure that the FDA could not agree to clinical trials "in which a human embryo is intentionally created or modified to include a heritable genetic modification." (Kaiser, 2019).

In many ways, the NAS report reproduces many aspects of the regime of normativity first established by *Splicing Life* in the way HGE has been framed as a problem (e.g. eugenic enhancement) and might be governed within the existing institutional framework. The only significant change was the much greater emphasis given to parental reproductive rights.

Reframing the issue in the UK

The UK debate was led by the Nuffield Council on Bioethics (NCoB), which produced a report on the general issues raised by GEd in 2016 (NCoB, 2016). This was followed by a separate study on "*Genome editing and human reproduction: social and ethical issues*" published in 2018 (NCoB, 2018), with a focus on the ethical acceptability of GEd for germline modification when used alongside other reproductive technologies.

The reproductive options facing couples were framed in terms of the desire to have a healthy child that is genetically related to both parents. The report then considered near-term and longer-term applications of GEd. It stated that cases in which it offers the only option of having a genetically related child are very rare (p45), but there were potentially many more situations in which the use of GEd could substantially increase the chances of success compared to PGD. Here GEd is clearly constructed as a reproductive technology.

The report also asserted that in the longer term there are other important possible uses of the technology, including the replacement of existing techniques such as PGD and new applications arising from whole genome sequencing. These include the exclusion of genetic factors that increase the risk of serious late onset disorders (p46). Going further, the report speculates about what a future could look like in which safe and effective GEd was available. Applications might include built-in genetic resistance to endemic disease, tolerance for adverse environmental conditions (e.g. as a result of climate change or in space flight), and "supersenses or superabilities" (p47). Surprisingly, these suggestions have strong similarities to tropes found in post-war reform eugenics.

GEd is then characterised as a generic enabling technology, similar to the steam train and the electronic computer which have been seen as revolutionary or age-defining: increasing productivity

spawning new industries and produce a rupture with what has gone before. ". . It is implicit that, in doing so, they reconfigure the social relations in which they are embedded." (p47). Here the co-evolution and mutual shaping of technological options and social norms is explicitly highlighted, reflecting the influence of critical social science ideas on the membership and work of the Council.

In considering the ethics of germline Ged, the Committee took an approach centred on human rights – as distinct from the principalism adopted in US inquiries. Within this framework the report concluded that the desire of parents to have genetically related children has positive social value. Furthermore, there is a strong moral claim that they should be allowed to pursue this interest without interference, including the use of GEd to produce children with genetic characteristics that improve their welfare (e.g. the absence of heritable disease). The Committee also examined how the development of germline GEd might affect social norms and social diversity, as well as the experience of disabled people. The overall conclusion was that germline GEd could be ethically acceptable provided it is consistent with, the welfare of a person who may be born and that any such interventions would uphold principles of social justice and solidarity (p vii). This discursive move completes the reframing of the technology as enabling parental reproductive rights.

In a final section on governance the Committee reviewed the established institutional arrangements that might regulate the development of germline GEd and recommended that: 1) Existing legal frameworks adequately covered the techniques of intergenerational GEd and should only be changed after "broad and inclusive societal debate"; 2) Research should be funded to inform the development of clinical applications and mechanisms established to ensure ongoing monitoring of outcomes before proceeding; 3) Germline GEd should be regulated by the HFEA and licensed on a case by case basis.

The NCoB report is a landmark in the international debate on human genetic engineering, setting out in detail a novel ethical justification for its development within the established regulatory framework that governed IVF and related technologies. It represents both the culmination of a series of incremental changes within the IVF regime of normativity, but also an important shift in the international discourse on this topic. In this context, the right of parents are placed clearly ahead of any fears about eugenics and GEd is clearly established as a reproductive technology.

The influence of this framework in clearly visible in the response to the birth of the first genetically modified babies using CRISPR in China in November 2018 which provoked international controversy. The US NAS and NAM, together with the UK's Royal Society, convened an international commission to develop guidelines on the Clinical Use of Human Germline Genome Editing. The report produced by the 18-member panel, which represented 10 nations was published in September 2020 (National Academy of Medicine, National Academy of Sciences, and the Royal Society, 2020). It recommended against creating a pregnancy with a human embryo which involved

germline modification until it was proven to be efficient, precise and safe. The Commission noted that these criteria have yet to be met. Should a country decide to permit the clinical use of the techniques, HGE should proceed incrementally and be limited to serious monogenic diseases. The Commission limited the use of germline editing to situations in which prospective parents: 1) have no other option for having a genetically related healthy child, or 2) where the expected proportion of unaffected embryos would be unusually low and have attempted at least one cycle of preimplantation genetic testing without success. Although, the Commission's recommendations suggest that a couple's desire to have a genetically related healthy child justifies the use of the technology, its criteria were more stringent than those proposed by the UK NCoB. Despite this, the overall framing of the development of germline genome editing is clearly placed within the regime of normativity established around IVF and articulated most clearly in the UK regulatory framework. This places parental reproductive rights as the overriding priority and frames GEd as a reproductive technology, distancing it from eugenics and making it ethically acceptable to develop.

9. Discussion and conclusion

This paper has charted how the idea of human genetic modification has been discursively constructed within two distinct regimes of normativity that have emerged around gene therapy in the USA and IVF in the UK over the last four decades. The concept of a regime of normativity has been developed to include not just scientific laboratory work but also the creation of new technologies and clinical practices, the design of artefacts and the development of commercial products. As described above, a regime of normativity conceived in this way is composed of the institutionalised formal and informal rules (e.g. shared beliefs and values, routines, regulations, practices) that mutually construct and are constructed by actors within a socio-technical system.

The analysis has shown how the constitution of these regimes has involved distinct and dynamic socio-technical processes, including the:

- Conceptual reframing of human genetic engineering from eugenics to therapeutics;
- Social negotiation of normative principles (e.g. the distinction between germline therapy, enhancement and eugenics) and the establishment of new rights (e.g. to have a healthy child);
- Discursive separation of acceptable/ unacceptable binary technical options (germline v somatic gene therapy; therapy v enhancement; the pre-embryo v embryo; reproductive v therapeutic cloning; mitochondrial v nuclear DNA);
- Blurring of boundaries (e.g. between IVF and genetic research);

- Institutional embedding of these principles and distinctions in codes of practice (e.g. RAC), research governance processes (e.g. HFEA) and product regulation (e.g. FDA);
- Building of different communities of promise including/ excluding specific group (e.g. the enrolment of patient in the UK; the dominance of scientists and clinicians in the USA);
- Construction of powerful moral-technical imaginaries and patient narratives to help mobilise support e.g. germline modification to treat inherited diseases;
- Creation of "demand" for the use of HGE and the growing influence of consumer/ patient rights discourses as the technology moved from the laboratory to the clinic/ marketplace.

Rather than focusing on purely discursive changes within bioethics and regulatory debates, the value of the concept of a regime of normativity is in highlighting the other processes (community building, institutional embedding, visioning) involved in establishing new governance frameworks around an emerging technology. This draws attention to actor strategies, institutional contexts and cultural resources that might enable or constrain the works of innovators.

This broader analytical approach has demonstrated how it became possible for human genetic engineering of future generations to move from an illegitimate idea associated with eugenics in the 1980s to a concrete proposal sanctioned by scientists and bioethicists in 2020. It has also provided an understanding of the important differences between countries.

National differences in institutions and politics

This paper suggests that a series of interlinked factors shape national regimes of normativity and the emerging frameworks governing germline GEd in the USA and UK. In particular, the different institutional contexts and politics of embryo research were critically important. In the USA, gene therapy emerged in clinical research on therapeutics and has been regulated as a medicinal product within a well-established and rigid structure that involves multiple agencies (e.g. FDA/ NIH). This has ensured that its development and governance has been kept firmly under the control of scientists and clinicians. Politically, proposals for germline GEd have been constrained by the influenced of anti-abortion groups opposed to embryo research and the community of promise supporting its development has not had sufficient influence to overcome this resistance. As a result of these institutional and political factors, there has been no major shift in the discursive framing of germline GEd, which has continued to be dominated by concerns about enhancement/ eugenics. By the end of 2020 there was little prospect of germline GEd being clinically tested in the USA in the near future, despite growing support from scientists and bioethicists.

In contrast, in the UK, IVF has not been governed as a medical therapy but within a novel and flexible framework involving a single centralised agency (HFEA). As a consequence, it has not been solely

controlled by professional group, and patients/ consumers have become influential actors in shaping policy. Politically, leading scientists were successful in building a broad community of promise involving patients that was sufficiently influential to overcome resistance from groups opposed to embryo research. This flexible regulatory structure allowed incremental changes to be made to policy and regulations and ultimately, the reframing of germline GEd as a reproductive technology. These shifts co-evolved with the articulation of a new discourse about the rights of parents to have a healthy child, which has overshadowed fears about genetic enhancement and designer babies. The pre-conditions now exist in the UK to allow the development of germline GEd within a tightly defined socio-technical niche. It is notable that it is this framework that has been drawn on in the recent international debate on clinical germline genome editing.

As somatic gene therapy becomes established in clinical practice and the use of IVF continues to grow, the transition from the laboratory to the clinic has normalised what were once highly contested procedures and closely linked them to the growth of new markets in the bioeconomy. This has provided powerful forms of validation and enabled a move from professionally dominated to a more consumer/ market-based form of governance to occur. It remains to be seen if germline GEd will follow this same path in the years to come, but many of the elements to enable the legitimate testing of this once controversial technology are now in place.

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