MITOCHONDRIAL REPLACEMENT THERAPY AND THE REGULATION OF REPRODUCTIVE GENETIC TECHNOLOGIES IN THE UNITED STATES

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ABSTRACT

The ability to alter the genes of future generations no longer belongs in the realm of science fiction. The genetic modification capabilities of modern science are advancing rapidly. Mitochondrial replacement therapy (MRT) represents the first crossing of the germline barrier in humans, and as of February 2015, it is the first procedure of its kind to be legalized in the Western world. How Congress decides to regulate MRT will influence future regulation of all genetic manipulation technologies. This brief argues that the current patchwork regulatory framework established in the United States is insufficient to deal with the complex issues MRT presents. As such, the creation of a new regulatory agency specifically focused on the oversight of reproductive and genetic biotechnologies may be necessary to balance the goals of ensuring the safety of research participants, promoting public debate, and stimulating continued scientific progress.

INTRODUCTION

The field of reproductive technology is renowned for pushing boundaries and contributing innovative approaches to the pursuit of fertility enhancement. *In vitro fertilization* (IVF), for example, was "recognized by a Nobel Prize in physiology and medicine . . . [which] all but vanquished the scourge of infertility."[1] Yet, with the convergence of reproductive sciences and genetic technologies, IVF is on its way to being supplanted by unprecedented breakthroughs that will transform reproductive medicine as

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[1] Eli Y. Adashi, *Fifty Years After Huxley: The Roadmap of Reproductive Medicine Revisited and Updated: The 2015 SRI-Pardi Distinguished Scientist Plenary Lecture of the Society of Reproductive Investigation*, 22 REPROD. SCI. 1330, 1330 (2015).

we know it.[2] These breakthroughs involve *germline modification*, a form of human genetic engineering that aims to alter the genes in sperm, eggs cells or embryos.[3] Unlike *somatic modifications*,[4] where changes in the genetic makeup die with their bearer, germline modifications affect every cell in the body, not only in the children that result from the procedure, but in all succeeding generations.[5]

In the face of such historic developments in our scientific capabilities, legislators must reexamine how to regulate the development and use of these innovations in the United States. This brief focuses on *mitochondrial replacement therapy* (MRT), which some deem a test case for the regulation of germline modification procedures.[6] MRT is a technique that prevents a host of severe neurological disorders caused by mutant mitochondrial DNA (mtDNA) by replacing it with healthy mtDNA extracted from donated eggs.[7] Because the changes are heritable, this procedure is a form of germline engineering. Although the technology has faced both praise and controversy,[8] the development of MRT is undeniably historic[9]:

> First, MRT represents the first ever crossing of the germline barrier. Second, MRT constitutes the first ever form of organelle, indeed whole cytoplasmic replacement therapy. Third, MRT represents the first ever gene therapy that is IVF based. Fourth, MRT serves as a regulatory test case for all future cutting-edge reproductive technologies. Fifth, MRT irrevocably alters the face of assisted reproduction from a discipline focused on infertility to one with a far broader portfolio.[10]

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[2] *See id.*

[3] *See Human Cloning and Genetic Modification: The Basic Science You Need To Know*, ASS'N OF REPROD. HEALTH PROF'LS 5, http://www.arhp.org/uploadDocs/cloning.pdf. (last visited Nov. 23, 2015) [hereinafter, *Ass'n of Reprod. Health*].

[4] *Id*. ("'Somatic' genetic engineering is genetic engineering that targets the genes in specific organs and tissues of the body of a single existing person without affecting genes in their eggs or sperm.").

[5] *Id.*

[6] Adashi, *supra* note 1, at 1332.

[7] Ruth L. Fischbach, Shawna Benston & John D. Loike, *Creating a Three-Parent Child: An Educational Paradigm for the Responsible Conduct of Research,* 15 J. MICROBIO. & BIO. EDUC. 186, 186 (2014).

[8] *See* Gretchen Vogel & Erik Stokstad, *U.K. Parliament Approves Controversial Three-Parent Mitochondrial Gene Therapy*, SCIENCE (Feb. 3, 2015, 2:00 PM), http://news.sciencemag.org/biology/2015/02/u-k-parliament-approves-controversial-three-parent-mitochondrial-gene-therapy.

[9] *See* Adashi, *supra* note 1, at 1332.

[10] *Id*.

This brief argues that the patchwork regulatory framework currently established in the United States is insufficient to deal with the complex issues at play. Instead, Congress should create a new regulatory agency to focus on the oversight of reproductive and genetic biotechnologies.

I. THE SCIENCE BEHIND MITOCHONDRIAL REPLACEMENT THERAPY

Our bodies are formed from a collection of cells, each containing forty-six chromosomes—tightly-packed groups of DNA that provide the blueprint for our development and functioning.[11] Each cell contains a nucleus that houses almost all our genetic material, and a mitochondrion, which acts as the cell's battery pack, using oxygen to create energy that powers the cell.[12] The mitochondrion also contains a small amount of its own genetic material, called *mitochondrial DNA* (mtDNA).[13] In reproduction, the egg and the sperm each carry half of the required number of chromosomes and combine their nuclear DNA to create a zygote, which divides to form an embryo.[14] mtDNA, however, is unique in that it is not created by a combination of its parents' cell DNA.[15] Instead, individuals inherit mtDNA exclusively from their mothers.[16]

Although mtDNA accounts for a very small percentage of the human genome, mitochondrial gene mutations can cause severe neurological consequences.[17] Mutant mtDNA "gives rise to a broad range of inborn errors of energy metabolism, the manifestations of which are highly disabling and often fatal."[18] More devastatingly, because mtDNA is passed on from the egg, all children from affected women inherit these mitochondrial mutations.[19]

MRT is a new fertility treatment that could prevent genetic diseases that stem from mutant mtDNA. The procedure works by removing the nuclear DNA from the target egg's defective mtDNA and placing it within a

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[11] J. Ravindra Fernando, Note, *Three's Company: A Constitutional Analysis of Prohibiting Access to Three-Parent In Vitro Fertilization*, 29 NOTRE DAME J. L. ETHICS & PUB POL'Y 523, 528 (2015).

[12] *Id.*

[13] Fischbach et al., *supra* note 7, at 187 ("Human beings have approximately 20,000 genes in their nuclear chromosomes and only about 35 genes in their mitochondria.").

[14] ASS'N OF REPROD. HEALTH, *supra* note 3, at 2.

[15] *See* Fischbach et al., *supra* note 7, at 187 (explaining that the mitochondria is located on the tail section of a sperm cell, which is broken off and excluded once the head portion, containing the nuclear DNA, successfully enters the egg).

[16] Fernando, *supra* note 11, at 529.

[17] Fischbach et al., *supra* note 7, at 186.

[18] Adashi, *supra* note 1, at 1331.

[19] Fischbach et al., *supra* note 7, at 186.

donated egg with healthy mtDNA.[20] The nuclear DNA of the donated egg is similarly removed so that the healthy mtDNA is the only contribution by the donor.[21] The need for MRT is apparent for families carrying mtDNA. While the treatment does little to help those currently living with mitochondrial disease, it allows the second generation transmission of mtDNA-based diseases to be circumvented.[22] For families carrying mtDNA, MRT is a source of hope for a future with genetically related children.

II. CONSIDERATIONS FOR SELECTING A REGULATORY FRAMEWORK FOR GERMLINE MODIFICATIONS IN THE UNITED STATES

A. MRT as a Regulatory Test Case

The significance of the resulting germline modification in MRT is small since mtDNA only "represents less than 0.2% of the total human genome."[23] The potential and perils of germline modification can be seen more vividly in other rapidly developing technologies such as ZFN, TALEN, CRISPR-Cas9 and ARCUS, which provide the ability to induce site-specific DNA changes in the genome.[24] However, this paper focuses on MRT as the regulatory test case for all future reproductive genetic technologies because a discussion of the regulatory regime behind MRT is both more relevant and salient. MRT represents the first ever crossing of the germline barrier in humans, and is the first procedure of its kind to be legalized in the Western world.[25]

In February 2015, both the House of Commons and the House of Lords in the United Kingdom overwhelmingly approved the use of MRT in humans,[26] making it the first country in the world to allow mitochondrial replacement therapy.[27] It has been noted that "[t]he regulatory adjudication of MRT in the United Kingdom, several years in the making, was exemplary in its focus on safety, ethics, and public receptivity."[28] With

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[20] Don P. Wolf, Nargiz Mitalipov & Shoukhrat Mitalipov, *Mitochondrial Replacement Therapy in Reproductive Medicine*, 21 TRENDS IN MOLECULAR MED. 68, 68-69 (2015).
[21] *Id.*
[22] *See id.*
[23] Fischbach et al., *supra* note 7, at 186.
[24] Hyongbum Kim & Jin-Soo Kim, *A Guide to Genome Engineering with Programmable Nucleases*, 15 NATURE REVS. GENETICS 321, 321 (2014).
[25] *See* Vogel & Stokstad, *supra* note 8.
[26] Adashi, *supra* note 1, at 1331.
[27] *See* Kashmira Gander, *World's First Three-Parent Baby Could Soon Be Born in UK, as Government Approves Treatment*, INDEPENDENT, Jul. 22, 2014, http://www.independent.co.uk/news/science/worlds-first-three-parent-baby-could-soon-be-born-in-uk-as-government-approves-treatment-9621572.html.
[28] Adashi, *supra* note 1, at 1331.

precedent set by the international community, and escalating pressure from within the country,[29] Congress must soon decide whether and how to regulate reproductive genetic technologies. Thus, Congress's treatment of MRT may lay the foundation for how advances in this field will be dealt with in the future.

B. Framing the Options and Criteria

For germline modification technologies like MRT, currently no "federal or state legislation specifically governs this advanced reproductive technology" in the United States.[30]

In this context, there are several regulatory pathways that may be adopted to provide oversight for germline modification technologies.

1. *Maintain the Status Quo*: The regulation of germline modification technology may be left to be regulated by market forces in the private sector.
2. *Cede Authority to the FDA*: Authority to regulate germline modification technologies may be granted to the FDA.
3. *Create a New Independent Regulatory Agency*: Congress could enact legislation authorizing the creation of a new regulatory agency focused specifically on the oversight reproductive and genetic biotechnologies.

If the regulatory treatment of MRT is to serve as a foundation for the regulation of future germline modification technologies, each of the possible alternatives available to Congress must be compared and tested. Although there may be a variety of relevant and important goals, this brief will focus on the ability of a regulatory framework to:

- Maximize safety and well-being for research participants.
- Encourage full and open debate.
- Ensure and enable the continued advancement of scientific progress.

The following sections will consider each of the presented regulatory alternatives individually against these three criteria.

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[29] Fernando, *supra* note 11, at 527.
[30] *Id.* at 526.

III. OPTION ONE: MAINTAINING THE STATUS QUO

The United States currently employs a patchwork system of oversight for reproductive genetic technologies.[31] There are "no federal law[s] or promulgated regulations directly addressing the genetic modification of gametes or early embryos" in humans.[32] Various aspects of reproductive research are covered by certain state laws.[33] Although without any formal regulatory authority, several NGOs and professional organizations in reproductive medicine have also set practice standards.[34] The only source of federal oversight comes from from the National Institute of Health (NIH) and the Food and Drug Administration (FDA).[35] The role of both these institutions in regulating reproductive technologies like MRT is both limited and uncertain.

The NIH, for example, considers the "social and ethical implications of 'novel gene-transfer research protocols,'" through the Recombinant DNA Advisory Committee (RAC).[36] However, RAC's mandate is limited to technology present in the 1980s, and thus, "it considers only those interventions that involve recombinant DNA."[37] As a result, because MRT involves cellular surgery rather than recombinant DNA, it technically falls outside the RAC's purview despite the fact that inheritable genetic modifications are involved.[38] Regardless, as a matter of policy, the RAC has stated that it will not review any proposals that involve the modification of gametes or embryos.[39] By refusing to review proposals, the RAC effectively cut off federal funding for germline modification research. In April 2015, the NIH more explicitly affirmed that heritable genetic modifications fall under the Dickey-Wicker Amendment, meaning that no federal funds will be made available for such research.[40] As a result of the current patchwork framework, the advancement and regulation of germline modification technology has essentially been left to market forces and the private sector.

The first option, and likely the easiest, is to maintain the status quo, leaving regulation to free-market forces. Several writers have suggested

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[31] Erik Parens & Lori P. Knowles, *Reprogenetics and Public Policy: Reflections and Recommendations*, 33 HASTINGS CTR. REP. S1, S10 (2003).
[32] Girard Kelly, Comment, *Choosing the Genetics of Our Children: Options for Framing Public Policy*, 30 SANTA CLARA HIGH TECH. L.J. 303, 336 (2014).
[33] Parens & Knowles, *supra* note 31, at S12.
[34] Kelly, *supra* note 32, at 336–339.
[35] Fernando, *supra* note 11, at 526–27.
[36] Kelly, *supra* note 32, at 337.
[37] Parens & Knowles, *supra* note 31, at S11.
[38] *See id.*
[39] Kelly, *supra* note 32, at 337.
[40] Editorial, *Gene Politics*, 523 NATURE 5, 6 (2015).

that, if left to the market, "most regulation will occur informally through the market interactions of willing consumers and providers of these services against a background of common law norms, some professional self-regulation, and occasional state legislative intrusions."[41] However, this patchwork approach is insufficient because it fails to adequately ensure safety and well-being, full and open public debate, and promote scientific progress.

A. The Private Sector and Safety & Well-Being

To leave the regulation of reproductive genetic research to the private sector may be dangerous for research participants and would place the United States in stark contrast with the approach taken by the rest of the world.[42] In the context of gene therapies, for example, researchers and clinicians have expressed concern that risks are taken in the private sector with little understanding of the long-term health consequences.[43] Unfortunately, experimental reproductive techniques have been rapidly introduced on the market "without sufficient prior animal experimentation, randomized clinical trials, or the rigorous data collection that would occur in federally funded studies."[44] As summarized by the National Conference of State Legislatures, "a substantial proportion of research and innovative therapy in reproductive medicine need not be subject to peer review, may not conform to current standards for informed consent, and may be offering services that have never been fully evaluated for safety and efficiency."[45] Germline modification technologies are rife with potential dangers, risks that have radical implications for the well-being of future generations. Such a technology demands a public system of oversight that "relies on more than the discretion of individual researchers and their institutions."[46]

B. The Private Sector and Public Debate

In addition to issues of participant safety, allowing the bulk of germline modification research to remain in the private sector is also "incompatible with the ideal of conducting such work in the light of forthright public deliberation."[47] The modification of heritable genes raises deep ethical questions and complex considerations regarding the well-being of families and society. The consequences of any side effects of such

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[41] *See* John A. Robertson, *Procreative Liberty in the Era of Genomics*, 29 AM. J.L. & MED. 439, 483–84 (2003).
[42] Parens & Knowles, *supra* note 31, at S11.
[43] *Id.*
[44] *Id.*
[45] *Id.*
[46] *Id.*
[47] *Id.* at S10.

treatment may not be foreseeable or expressed until years into the child's life or perhaps generations down the line. In addition to the risks of these procedures to subsequent generations, innumerable challenging questions arise that cannot be fully answered by science. What sort of procedures do we consider moral? How do we deal with other countries with different values and should we be concerned about keeping up with the technological advancements of other nations? How do you respect the autonomy of those who consent and willingly engage in such research despite the risks and can parents' consent on behalf of their unborn children?[48] How do we ensure equal access to such technology and avoid situations of exploitation and social injustice?[49] How do we address concerns regarding the potential rise of designer babies and eugenics?[50]

We, as a society, must decide what risks we are willing to accept and where we draw the line. "[S]ince scientists are members of a democratic community who share resources (and all researchers in this country benefit directly or indirectly from our extraordinary scientific infrastructure), they are obliged to subject their research to public scrutiny."[51] A decision as important as whether to allow inheritable genetic modification should not be left to individual researchers and the private sector.

C. The Private Sector and Scientific Progress

Finally, the natural secrecy of the private sector may impede the progression of germline modification research.[52] Without public funding, research and innovation will remain in the hands of the private industry, who have no incentive to share the fruits of their labor. With the potential that germline modification technologies hold for saving lives and curing a host of genetic diseases, public research in this field should be promoted. Some will argue that the financial incentives of an unregulated free-market will result in the most technological advancement. However, incentives to cut corners and accept greater risks in the private sector may eliminate the therapeutic and financial rewards of germline modifications. Jesse Gelsinger is a vivid example.

Jesse Gelsinger suffered from ornithine transcarbamylase deficiency (OTC), a rare metabolic disorder that prevented the body from

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[48] *See* Joanna Smolenski, *CRISPR/Cas9 and Germline Modification: New Difficulties in Obtaining Informed Consent*, 15 AM. J. BIOETHICS 35, 35-68 (2015).
[49] *See* Parens & Knowles, *supra* note 31, at S7.
[50] *Id*.
[51] *Id.* at S11.
[52] *See id.* at S10.

breaking down ammonia.[53] He died in 1999 during a gene-therapy experiment gone wrong at the University of Pennsylvania.[54] In the 1990s, the ability of gene therapy "to cure was thought to be boundless and the hype was astronomical" as companies invested millions of dollars in the technology.[55] Yet, after a series of revelations regarding serious deficiencies in informed consent and study design, progress in gene therapy stalled as public opinion and trust collapsed. "Gene therapy remains an obvious route to treat OTC . . . [b]ut the memory of what happened to Gelsinger has slowed progress in gene therapy for any condition."[56]

Just like pharmaceutical and the biotech industries, clinical trials are the lifeblood of reproductive technologies. Profit driven motives to cut corners on informed consent and safety precautions in order to access human test subjects increases the likelihood of tragedies such as Jesse Gelsinger. Contrary to the financial interests of the private sector, avoidable failures could stymie research in germline modification for decades. In order to promote technological advancement, and to unlock both the financial and therapeutic potential it offers, more robust and regulated safety precautions must be put in place to protect the "fragile nature of the public trust that sustains research."[57]

IV. OPTION TWO: THE FOOD AND DRUG ADMINISTRATION

The authority to regulate germline modification technologies could be ceded to the FDA. The FDA has already asserted its jurisdiction over MRT through the Office of Cellular, Tissue, and Gene Therapies of the Center for Biologics Evaluation and Research.[58] This branch of the FDA's task is to oversee "human cells used in therapy involving the transfer of genetic material by means other than the union of gamete nuclei."[59] The FDA's claim to MRT rests upon the therapy's inclusion under the broad definition of a "drug."[60] A "drug" is defined by the Food, Drug, and

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[53] Osagie K. Obasogie, *Ten Years Later: Jesse Gelsinger's Death and Human Subjects Protection*, THE HASTINGS CENTER: BLOG (Oct. 22 2009), http://www.thehastingscenter.org/ten-years-later-jesse-gelsingers-death-and-human-subjects-protection.

[54] *Id.*

[55] *Id.*

[56] *See* Editorial, *Gene-Therapy Trials Must Proceed with Caution*, 534 NATURE 590, 590 (2016).

[57] Mark Yarborough & Richard R. Sharp, *Public Trust and Research a Decade Later: What Have We Learned Since Jesse Gelsinger's Death?*, 97 MOLECULAR GENETICS & METABOLISM 4, 4 (2009).

[58] Glenn Cohen, Julian Savulescu & Eli Y. Adashi, *Transatlantic Lessons in Regulation of Mitochondrial Replacement Therapy*, 348 SCI. 178, 179 (2015).

[59] *Id.*

[60] Kelly, *supra* note 32, at 342.

Cosmetic Act to encompass anything that is "intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease," or that is "intended to affect the structure or any function of the body."[61] Although this option can ensure the safety and efficacy of research participants, ceding authority to the FDA may not be the best option as it falls short in its ability to consider well-being, promote public debate, and ensure continued scientific progress.

A. The FDA and Safety & Well-Being

The advantage for ceding authority to the FDA is that it already exists and it is arguably ready to exercise oversight, at least on safety and efficacy grounds. Under the FDA's existing regulations, approval of MRT for therapeutic use will require "phased clinical trials pursuant to an Investigational New Drug application (IND)."[62] To gain the FDA's approval, the technology will be subject to a "searching review of the method's safety and efficacy as well as satisfactory completion of human trials."[63] Thus, regulation of MRT by the FDA would provide significantly more comprehensive oversight in ensuring the safety of research participants.

On the other hand, because the FDA's mandate is limited to issues related to safety and efficacy, considerations regarding the "well-being" of the research participants and of society will be neglected under the FDA's authority.[64] As discussed above, this is significant because the modification of heritable genes raises deep ethical questions and considerations regarding the well-being of families and society. For example, germline modification techniques such as MRT permanently change the mtDNA in every cell of the resulting child,[65] unlike normal drugs where the doses can be slowly increased and stopped in the event of a serious side effect. The consequences of any side effects may not be foreseeable or expressed until years into the child's life. As such, classifying MRT as "drugs likely encompasses too broad of a definition and offers inadequate regulation for a drug that would change the structure and function of the human body."[66] It would be best if technologies like MRT did not fall exclusively within FDA's mandate.[67]

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[61] *Id*. at 342-43.
[62] *Id.* at 337–38.
[63] Fernando, *supra* note 11, at 526–27.
[64] Kelly, *supra* note 32, at 345–46.
[65] *See* ASS'N OF REPROD. HEALTH, *supra* note 3, at *5.
[66] Kelly, *supra* note 32, at 343.
[67] Parens & Knowles, *supra* note 31, at S12.

Congress may choose to remedy this by endowing the FDA with the power to consider moral and philosophical issues of the technology.[68] To do so will require Congress to expand the FDA's regulatory authority without distorting its current three-tier classifications.[69] Such a radical change would require reorganization of the agency and its members.[70] With the complexity and expenses related to such reorganization in mind, it would make more sense for Congress to focus its resources on creating a new independent agency and framework for oversight.[71]

B. The FDA and Public Debate

Due to the complex and controversial nature of genetic modification, decisions regarding germline modification should be informed by collaborative public discussions on both safety and well-being concerns.[72] In this respect, the FDA is also severely lacking. In the United States, discussions regarding MRT have been limited to a few conversations among experts, with relatively little input from the public.[73] In fact, the FDA has never officially even considered clinical trials for MRT. The only time it was discussed was in early 2014 during a discussion regarding "oocyte modification" by the FDA's Cellular, Tissue, and Gene Therapies Advisory Committee.[74] No official conclusion from the meeting was ever provided and the results were merely summarized by the chairman with the brief comment that "[s]everal panelists felt 'there was probably not enough data in animals . . . to move on to human trials without answering a few additional questions.'"[75] The FDA has also commissioned the committee of the Institute of Medicine to provide an ad hoc review of the ethical and social considerations of novel approaches to treating mitochondrial DNA diseases.[76] However, "only two of the planned committee sessions will be available to the public."[77]

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[68] Kelly, *supra* note 32, at 345–46.
[69] *See id.* at 344–46.
[70] *Id*.
[71] *Id*.
[72] *See* Mark S. Frankel and Audrey R. Chapman, *Human Inheritable Modifications: Assessing Scientific, Ethical, Religious, and Policy Issues*, AM. ASS'N FOR THE ADVANCEMENT OF SCI., Sept. 2002, at 3–5, https://www.aaas.org/sites/default/files/migrate/uploads/germline.pdf.
[73] Cohen et al., *supra* note 58, at 179.
[74] *Id*.
[75] *Id*.; *see also* Sharon Begley, *U.S. FDA Weighs Evidence on Producing 'Three-Parent' Embryos*, REUTERS (Feb. 25, 2014), http://www.reuters.com/article/us-usa-health-ivf-idUSBREA1O1WL20140225.
[76] Cohen et al., *supra* note 58, at 179.
[77] *Id*.

C. The FDA and Scientific Progress

Finally, the FDA's recent actions have done little to create confidence in its ability to foster safe but productive research in this field. As mentioned, MRT was largely ignored in a brief discussion by the FDA's Cellular, Tissue, and Gene Therapies Advisory Committee in 2014.[78] No further FDA action is expected until the Institute of Medicine report has been released, which is estimated to be around early 2016.[79] Meanwhile, "any relevant INDs submitted would remain on hold."[80]

In terms of the goal of promoting scientific progress, the FDA is not the ideal option for regulating germline modifications because it is not efficiently structured to deal with novel fields that are developing as rapidly as reproductive genetics. This stems from the fact that the FDA's mandate is both too broad and too narrow. The FDA's authority is too broad because it encompasses all therapeutics. For example, even the FDA Office of Cellular, Tissue, and Gene Therapies—the designated proximate overseer of MRT—is entrusted with a diverse portfolio of cellular, tissue, and gene therapeutics. [81] On the other hand, FDA's authority is too narrow for it extends only to (i) drugs, (ii) biologics and (iii) and devices.[82] Thus, the FDA must proceed on the premise that MRT constitutes a drug or a biological product.[83] In other words, novel scientific advances must be manipulated and jerry-rigged to fit the FDA's current and outdated three-category framework. The necessity of having to classify every potential genetic engineering technology as a drug, biologic, or device is a regulatory challenge and creates an environment of uncertainty. The resulting confusion may have a chilling effect among scientists and investors who shy away from potential breakthroughs due to the unpredictability of whether the FDA will exert jurisdiction over new technologies and under which category it will be classified. By stunting investment and critical scientific research, the U.S. risks losing its edge and its market share to areas with more fluid and predictable regulations such as the UK.[84]

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[78] *Id*.
[79] *Id*.
[80] *Id*.
[81] Kelly, *supra* note 32, at 342.
[82] *See id.* at 342–43.
[83] *Id*.
[84] *See* Christopher J.P. Velis, *Ambiguity from FDA Stunts Growth in the US, While Innovation Flourishes in Europe*, REG. AFF. PROF. SOC'Y (Jul. 23, 2013), http://www.raps.org/Regulatory-Focus/Features/Transfered-Features/2013/07/23/9202/Ambiguity-from-FDA-Stunts-Growth-in-the-US-While-Innovation-Flourishes-in-Europe/.

V. OPTION THREE: A NEW INDEPENDENT REGULATORY AGENCY

Congress could enact legislation authorizing the creation of a new regulatory agency focused specifically on the oversight of reproductive and genetic biotechnologies. This would be comparable to agencies that exist in other countries such as the Assisted Human Reproduction Agency (AHRA) in Canada and the Human Fertilisation and Embryology Authority (HFEA) in the United Kingdom.[85]

The creation of an independent agency addresses many of the shortcomings of the current patchwork regulation in the U.S. and of ceding oversight authority to the FDA. Thus, it may be the best option to maximize the safety and well-being of research participants, promote public debate, and ensure the continued advancement of scientific progress in the United States. The recent "exemplary" success of the "regulatory adjudication of MRT" by the HFEA is illustrative of the capacities of an independent agency.[86] The UK regulatory experience may also provide invaluable insight into how a similar agency in the United States could be structured.

A. The New Agency and Safety & Well-Being

First, the creation of an independent regulatory agency will better maximize the safety and well-being of research participants. An agency tasked with the responsibilities and regulatory authority of an IRB would be able to adequately perform scientific and ethical reviews of all germline research protocols and procedures.[87] In addition, the "new agency could be authorized to directly consider policy concerns that extend beyond the FDA's purview of safety and efficacy."[88] By appointing individuals with more specialized expertise, a new agency will be more competent than the FDA in dealing with the complex array of social, ethical, and legal issues implicated by germline modifications.[89]

The success of such an independent regulatory agency has been demonstrated by the HFEA in the United Kingdom. The HFEA is responsible "for licensing and monitoring clinics and laboratories involved in gamete or embryo storage, creation, or use, and the act sets out the purposes for which licenses will be required . . . ."[90] The HFEA establishes and publishes a code of practice that acts as a source of guidance for

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[85] *See* Erin L. Nelson, *Comparative Perspectives in the Regulation of Assisted Reproductive Technologies in the United Kingdom and Canada*, 43 ALBERTA L. REV. 1023, 1023 (2006).
[86] Adashi, *supra* note 1, at 1331.
[87] Kelly, *supra* note 32, at 344-46.
[88] *Id.*
[89] *See id*.
[90] Parens & Knowles, *supra* note 31, at S15.

patients, clinics, and clinicians as to the proper conduct of actions carried on under a HFEA license.[91] "Through the setting of standards and the provision of licenses, the HFEA provides both quality control and assurances that ethical conduct in embryo research is maintained."[92] If the U.S. creates a similar independent agency with the ability to oversee germline research and clinical application at a federal level, the government will be able to better ensure both scientific quality assurance and greater certainty that ethically unacceptable activities will not be conducted behind the closed doors of the private sector.

B. The New Agency and Public Debate

The limited interaction between private institutions and the FDA with the public stands in stark contrast to what can be accomplished by an independent regulatory agency. For example, the difference between the relative weight assigned to public consultation on regulatory issues by the FDA and the HFEA is staggering. In the UK, the "public consultation process was an extensive outsourced multimethod (e.g., surveys and workshops) effort on a national scale lasting 6 months,"[93] and has been praised to be "nothing short of exemplary in its focus on safety, ethics, and public receptivity."[94] The vetting process in the United States, on the other hand, has been described as "a work in progress."[95]

The flexibility provided by the creation of a new independent regulatory agency can be used to establish a system that can foster the discussion of safety and well-being concerns with the greater public. This is particularly important in the United States, where the lack of uniform oversight for reproductive technologies can be partially attributed to the deep and divisive debate around the issue of abortion.[96] In the backdrop of the polarizing and volatile dynamics of this debate, many policymakers have been reluctant to join the conversation, which has greatly hampered the regulation and advancement of assisted reproductive technologies.[97]

If reproductive genetic research is to be taken seriously, both sides must begin to join the conversation and find way to compromise. Discussions regarding MRT can no longer be isolated to select experts in the FDA or relegated to individual researchers and their private financial backers. A new independent agency separate from the political arena with a

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[91] *Id.*
[92] *Id.*
[93] Cohen et al., *supra* note 58, at 180.
[94] Adashi, *supra* note 1, at 1331.
[95] *Id.*
[96] *See* Parens & Knowles, *supra* note 31, at S11.
[97] *Id.*

diverse board along the lines of the HFEA will help ensure that the concerns of both sides of the abortion debate are taken seriously.[98] Members of the board may be appointed by a bipartisan committee, with representation from all of the stakeholders involved.[99] Such an independent agency will allow engagement with the public, increase understanding, and build consensus among traditionally hostile groups.

C. The New Agency and Scientific Progress

Despite the traditional belief that more regulations result in greater restrictions on innovation, a new regulatory agency would likely accelerate future research and development of reproductive genetic technologies. Several lessons can be drawn from the UK regulatory paradigm regarding the continued progress of scientific advancement. Clinical trials in the UK began as early as October 2015, whereas the FDA has essentially put a stop to all MRT research in the United States.[100]

1. Specialized and Expert Nature

First, the HFEA is a specialized agency whose sole charge is to regulate reproductive technologies.[101] Thus, the HFEA was more capable and expert in their treatment of MRT, which was viewed "as a circumscribed outgrowth of related and highly familiar technologies (e.g., in vitro fertilization) rather than as a therapeutic." [102]

The creation of a new independent agency in the United States would allow the appointment of individuals with more specialized expertise who will be more competent than the FDA in dealing with the complex array of social, ethical, and legal issues implicated by germline modification technologies.[103] Further, germline modification research would no longer need to be manipulated and interpreted to fit into the FDA's existing three-category framework.

2. Ability to Foster National Pride

Second, MRT research was a tremendous source of pride in the UK.[104] "For better or worse, the parliamentary debate has proceeded with an air of national pride. Even those opposed to MRT noted their admiration for the world-class work . . . ."[105] One commentator believed "that this national

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[98] *See id.* at S19.
[99] *Id*.
[100] Cohen et al., *supra* note 58, at 179.
[101] *See* Parens & Knowles., *supra* note 31, at S15.
[102] *See* Cohen et al., *supra* note 58, at 179.
[103] *Id.*
[104] *Id.* at 180.
[105] *Id.*

sense of pride may have swayed some votes in support of MRT."[106] Despite the fact that researchers in the United States have made equally important discoveries in this area, American scientists have not enjoyed the same fanfare.[107] A new regulatory agency could potentially accelerate future research and development of germline modification technologies, if national attention can be brought to the issue, which has previously remained largely inaccessible to the general public.[108]

3. Flexibility to Deal with Novel Innovations

Third, the HFEA was provided with the mechanisms necessary to deal with new innovations and novel application of existing technologies. For example:

> The authority of the HFEA to grant licenses is limited by the purposes described in the act. The decision to articulate the purposes of embryo usage rather than specific techniques has ensured that the act can incorporate novel techniques that were not envisaged when the act was drafted. In addition, if new techniques and applications merge that fall outside the HFEA's statutory authority, the act allows parliament to expand the range of purposes that are placed under the HFEA's authority, thereby ensuring that new purposes do not call for new oversight agencies and preserving the integrity of the system.[109]

Recognizing that it may be nearly impossible to keep pace with scientific and technological developments, Congress should consider providing the new independent agency in the United States with similar mechanisms to accommodate and adapt to contemporary developments in technology, information and public opinion.

4. Clarity

Finally, a national and specialized agency would provide clear and unified regulatory guidance. Germline modification research would no longer need to be manipulated and interpreted to fit into the FDA's existing three-category framework. The bureaucratic roadblocks that result from the current patchwork of oversight between the FDA, NIH, independent agencies and state legislation could be avoided.

Additional steps may be taken to further ensure clarity. For example, the HFEA publishes a code of practice to provide information to "patients, clinics, and clinicians alike" as to the "proper conduct of activities

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[106] *Id.*
[107] *Id.*
[108] Kelly, *supra* note 32, at 345.
[109] Parens & Knowles, *supra* note 31, at S15-16.

carried on in pursuance of a license . . . ."[110] Thus, the HFEA is not seen as merely a regulatory roadblock to be overcome, but as a source of guidance.

> The support in the United Kingdom for the HFEA extends to the scientific and regulatory communities, which appear to have worked out a cooperative relationship. When a clinic cannot be licensed due to insufficient standards or protocols, the HFEA works with that clinic to ensure that it understands what is required to successfully apply for a license. Despite the comprehensive and highly centralized regulation, the United Kingdom remains committed to scientific freedom, and arguably has one of the most liberal embryo research policies in the world."[111]

A new independent agency in the United States could similarly provide clarity and promote cooperation through the development of a code of practice designed to guide and educate patients, researchers, and clinicians. A more predictable system will encourage investment and ensure that the U.S. does not fall behind in the advancement of scientific progress.

CONCLUSION

It is clear that the regulatory treatment of germline modification technologies in the U.S. and the U.K. have diverged significantly.[112] Questions about why these differences exist, whether they should they exist and what it means for some hypothetical future innovation, can no longer be dismissed as academic exercises. The future has arrived and "MRT represents but one of a growing complement of novel reproductive technologies, many of which will require expert regulatory adjudication."[113] With precedent set by the international community and escalating pressure from within the country,[114] Congress must soon decide whether and how to regulate MRT. Its decision may lay the foundation for how all advances in this field will be dealt with in the future.

The current patchwork of regulations and the FDA are both ill-equipped to deal with the complex issues involved. Instead, Congress should consider enacting legislation to authorize the creation of a new regulatory agency focused specifically on the oversight of reproductive and genetic biotechnologies. The process will not be easy but the results may well be worth the effort. The bedrock formed by clear and unified regulatory guidance would allow for the maximization of safety and well-being for research participants and patients, foster much needed public

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[110] *Id.* at S15.
[111] *Id.* at S16.
[112] *See* Cohen et al., *supra* note 58, at 179.
[113] *Id.*
[114] Fernando, *supra* note 11, at 527.

conversation, and stimulate scientific progress in a crucial field at the cutting-edge of science.