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Myrisha S. Lewis

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SEGMENTED INNOVATION IN THE LEGALIZATION OF MITOCHONDRIAL TRANSFER: LESSONS FROM AUSTRALIA AND THE UNITED KINGDOM

Myrisha S. Lewis*

*Associate Professor, William & Mary Law School; J.D., Columbia Law School; A.B., Harvard College. For helpful comments and suggestions, I thank Aaron Bruhl, Layla Cachalia, Evan Criddle, and participants at the *Houston Journal of Health Law and Policy*'s 9th Annual Symposium. Nicole Bemberis, Leanna Gibson, Kate Halkias, Anna Jacobeen, Majesta-Doré Legnini, and Jayde Morgan provided excellent research and citation assistance.

ABSTRACT

The U.S. is often characterized as a leader in innovation—a home of Nobel Prize-winning scientists, innovators, and abundant research funding. Yet, in the area of assisted reproduction combined with genetic modification or substitution, what I call "reproductive genetic innovation," that characterization begins to wane. This Article focuses on the regulation of mitochondrial transfer, a subset of reproductive genetic innovation. While human clinical trials related to mitochondrial transfer go forward in the U.K., the clinical use of the technique remains illegal in the U.S. due to a system of subterranean regulation by the U.S. Food and Drug Administration and a now-recurring federal budget rider.

In the U.K., the government structured and carried out a public consultation as part of the legalization of mitochondrial transfer. Recently, Australia announced a plan to consider the potential legalization of mitochondrial transfer. In August 2021, the Australian federal government completed a public-facing step in implementing a gradual approach to considering the legalization of mitochondrial transfer, and in March 2022, Maeve's Bill passed in the Australian Parliament.

This Article draws on the experiences of two common-law countries, the United Kingdom and Australia, to identify potential avenues for a gradual approach to legalizing mitochondrial transfer in the United States. Progress on mitochondrial transfer could start a broader American discourse that could facilitate access to mitochondrial transfer and the other techniques in the area of reproductive genetic innovation.

INTRODUCTION

The United States is a leader in science and innovation. Recent data shows that the United States spends more on research and development than any other country in the world.[1] Yet, the United States' research spending lead has narrowed over the years.[2] Currently while the U.S. is ranked first in research and development spending, China is second, the United Kingdom is seventh , and Australia is thirteenth.[3]

The United States has been a leader in other areas of technological and medical innovation, but it lags the U.K, not only in insurance coverage of fertility treatments but also in terms of the pace of innovation.[4] A few years ago, mitochondrial transfer—a technique that combines in vitro fertilization (IVF) with genetic substitution—was the subject of significant media attention, especially as the United Kingdom debated and ultimately legalized the use of the technique.[5] As will be detailed in Part I, mitochondrial transfer could not only improve fertility outcomes but also prevent the transmission of harmful genetic diseases like Leigh Syndrome that have severe

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[1] JOHN F. SARGENT JR., CONG. RSCH. SERV., R44283, GLOBAL RESCH. & DEV. EXPENDITURES: FACT SHEET 2 (2020), https://crsreports.congress.gov/product/pdf/R/R44283/13; Mark Boroush, *Research & Development: U.S. Trends and International Comparisons*, NAT'L SCI. BD. (Jan. 15, 2020), https://ncses.nsf.gov/pubs/nsb20203/cross-national-comparisons-of-r-d-performance.

[2] SARGENT JR., *supra* note 1, at 1.

[3] *Id.* at 2.

[4] For more on insurance coverage for ART, *see e.g.,* June Carbone & Naomi Cahn, *Embryo Fundamentalism*, 18 WM. & MARY BILL RTS. J. 1015, 1031–32 (2010); BRYCE H.P. MENDEZ, CONG. RSCH. SERV., IF11504, INFERTILITY IN THE MILITARY (2021), https://crsreports.congress.gov/product/pdf/IF/IF11504.

[5] Mitochondrial transfer is also referred to as "mitochondrial replacement therapy" or "mitochondrial donation therapy." Brittany Shoot, *3-Parent IVF: Why Isn't It Available in the United States?*, THE GUARDIAN (Feb. 27, 2015, 8:22 PM), https://www.theguardian.com/sustainable-business/2015/feb/27/3-parent-ivf-us-mitochondria-dna-babies [https://perma.cc/RHM9-96VA]; Julian Savulescu, *Mitochondrial Disease Kills 150 Children a Year. A Micro-Transplant Can Cure It.*, THE GUARDIAN (Feb. 2, 2015), https://www.theguardian.com/science/2015/feb/02/mitochondrial-transfer-micro-transplant-parliamentary-debate; Rafqa Touma, *Mitochondrial Donation: How an IVF Procedure Could Help Australian Families 'Break the Genetic Chain'*, THE GUARDIAN (June 5, 2021, 4:00 PM), https://www.theguardian.com/australia-news/2021/jun/06/mitochondrial-donation-how-an-ivf-procedure-could-help-australian-families-break-the-genetic-chain.

negative impacts on organs such as the brain, heart, and kidneys.[6] Mitochondrial transfer continues to inhabit the scientific and popular spheres, as babies continue to be born as a result of the technique in Ukraine, Greece, and Mexico.[7] This Article focuses on the experiences of the United Kingdom and Australia in the legalization of mitochondrial transfer.[8] In doing so, the Article contributes to the assisted reproductive technology ("ART"), innovation, administrative law, and drug law literatures.[9]

Mitochondrial transfer, a technique that combines IVF with genetic substitution, has been legalized for human clinical research and use in the United Kingdom while the technique remains effectively banned in the United States by both FDA and

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[6] *Leigh Syndrome*, GENETICS HOME REFERENCE (Aug. 17, 2020), https://ghr.nlm.nih.gov/condition/leigh-syndrome#genes; *see infra* Part I.(A); *see also* Emily Mullin, *The Fertility Doctor Trying to Commercialize Three-Parent Babies*, MIT TECH. REV. (Jun. 13, 2017), https://www.technologyreview.com/2017/06/13/151273/the-fertility-doctor-trying-to-commercialize-three-parent-babies/; U.S. FOOD & DRUG ADMIN., TRANSCRIPT OF CENTER FOR BIOLOGICS EVALUATION AND RESEARCH BIOLOGICAL RESPONSE MODIFIERS ADVISORY COMMITTEE OPEN SESSION MEETING #32, 42, 77, 134, 226 (2002) [hereinafter MEETING #32 TRANSCRIPT]; Jason Barritt et al., *Epigenetic and Experimental Modifications in Early Mammalian Development: Part II Cytoplasmic Transfer in Assisted Reproduction*, 7 HUM. REPROD. UPDATE 428, 433–34 (2001); Alice Park, *Experts Are Calling for a Ban on Gene Editing of Human Embryos. Here's Why They're Worried*, TIME (Mar. 13, 2019, 2:22 PM), https://time.com/5550654/crispr-gene-editing-human-embryos-ban/; Henry T. Greely, *CRISPR'd Babies: Human Germline Genome Editing in the 'He Jiankui Affair'*, 6 J. L. & BIOSCIENCES. 111, 114 (2019) ("not all human germline genome editing must be embryo editing. One could take eggs and sperm from people and, *ex vivo*, edit them before using these edited gametes to create an embryo, rather than edit the embryo itself.").

[7] *See, e.g.*, Tetsuya Ishii & Yuri Hibino, *Mitochondrial Manipulation in Fertility Clinics: Regulation and Responsibility*, 5 REPROD. BIOMEDICINE & SOC'Y ONLINE 93, 93 (2018) ("It was found that regulation of the clinical use of [mitochondrial manipulation techniques] could be broken down into three categories: (i) largely prohibited (USA and China), (ii) not regulated (Northern Cyprus and Ukraine), and (iii) insufficiently regulated (the remaining 12 countries, including Mexico)."); *see also* Emily Mullin, *Patient Advocates and Scientists Launch Push to Lift Ban on 'Three-Parent IVF'*, STAT NEWS (Apr. 16, 2019), https://www.statnews.com/2019/04/16/mitochondrial-replacement-three-parent-ivf-ban/; Bianca Nogrady, *Australia Moves a Step Closer to 'Three-Person IVF'*, NATURE (June 29, 2018), https://www.nature.com/articles/d41586-018-05451-z; Erik Robinson, *Long-Term Study of Mitochondrial Replacement Therapy in Monkeys Finds No Adverse Health Effects*, OHSU: NEWS (Dec. 8, 2020), https://news.ohsu.edu/2020/12/08/long-term-study-of-mitochondrial-replacement-therapy-in-monkeys-finds-no-adverse-health-effects.

[8] Shoot, *supra* note 5; Savulescu,*supra* note 5; Touma, *supra* note 5.

[9] *See* discussion *infra* in Parts I.B and III.C.

Congressional action.[10] Regulatory progress has essentially stalled in the United States, and there is little hope for imminent change. On the topic of the progress (or lack thereof) of mitochondrial transfer in the U.S., Dr. Eli Adashi has noted "It was really an American idea…[w]hich makes it all the more unfortunate that it has been restricted here."[11]

While the U.S. regulatory system remains at a standstill with minimal inquiry into mitochondrial transfer, Australia has been engaged in a public inquiry since 2018. In 2021, after hearing the story of a 5-year-old girl named Maeve Hood who was diagnosed with Leigh Syndrome, a debilitating form of mitochondrial disease, a Victorian Parliament member introduced "Mitochondrial Donation Law Reform (Maeve's Law) Bill 2021" in the Australian Senate, hereinafter referred to as "Maeve's bill."[12] Maeve's bill is based on the U.K.'s legislation legalizing mitochondrial transfer.[13] The Australian Health Minister, Greg Hunt, supported the law, as did the

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[10] *See* Lyria Bennett Moses, *Understanding Legal Responses to Technological Change: The Example of In Vitro Fertilization*, 6 MINN. J.L. SCI. & TECH. 505, 506-07 (2005); Emily Mullin, *Pregnancy Reported in the First Known Trial of "Three-Person IVF" for Infertility*, STAT NEWS (Jan. 24, 2019) https://www.statnews.com/2019/01/24/first-trial-of-three-person-ivf-for-infertility/; *Mitochondrial Donation Treatment*, HUM. FERTILISATION & EMBRYOLOGY AUTH., https://www.hfea.gov.uk/treatments/embryo-testing-and-treatments-for-disease/mitochondrial-donation-treatment/ [hereinafter HUM. FERTILISATION & EMBRYOLOGY AUTH.]; *Louise Brown: World's First IVF Baby's Family Archive Unveiled*, BBC NEWS: BRISTOL (July 25, 2018), https://www.bbc.com/news/uk-england-bristol-44940929; *Mitochondrial Donation Law Reform (Maeve's Law) Bill 2021*, Public Hearing Transcript, THE SENATE CMTY. AFFS. LEGIS. COMM. (Aug. 6, 2021), https://www.aph.gov.au/Parliamentary_Business/Committees/Senate/Community_Affairs/MitochondrialLawReform/Public_Hearings [hereinafter *Public Hearing Transcript*] (noting that there may not be confirmation from the UK. Government when or if a pregnancy is achieved because of mitochondrial transfer).

[11] Radhika Viswanathan, *3 Biological Parents, 1 Child, and an International Controversy*, VOX (Jul. 28, 2018, 10:00 AM), https://www.vox.com/2018/7/24/17596354/mitochondrial-replacement-therapy-three-parent-baby-controversy.

[12] Emily McPherson, *How a Five-Year-Old Girl Inspired Proposed DNA Donation Laws*, 9 NEWS (Mar. 24, 2021, 1:26 PM), https://www.9news.com.au/national/mitochondria-disease-explainer-how-a-five-year-old-girl-inspired-proposed-new-dna-donation-laws/03d5dd35-2c65-4157-841b-56b486bd0013; *see Making a Law in the Australian Parliament*, PARLIAMENTARY EDUC. OFF., https://peo.gov.au/understand-our-parliament/how-parliament-works/bills-and-laws/making-a-law-in-the-australian-parliament/ (explaining that "[a] bill can only become a law if it is passed by a majority vote in the Senate and the House of Representatives.").

[13] McPherson, *supra* note 12.

International Society for Stem Cell Research (ISSCR).[14] In December 2021, Maeve's bill passed in the Australian House of Representatives and in March 2022, it passed in the Australian Senate.[15] Maeve's law commenced on October 1, 2022.[16]

In previous articles, I have argued for the legalization of mitochondrial transfer in the United States.[17] This Article continues that argument and focuses on ways to use public deliberation in furtherance of that legalization. As such, the Article identifies those tools of deliberative democracy that have been successful in other countries, as they may prove useful in response to American (and foreign) scientists' continued calls for a public discourse related to genetic modification.[18] If societal discourse will impact regulatory decisions such that the lack of a societal discourse or widespread acceptance will continue to lead to an effective ban on reproductive genetic innovation, then society will need to decide whether to have that discussion and how that discussion would even be structured if it did occur.[19] The U.K. and Australian experiences could also be part of

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[14] *Id.*; Letter from Melissa H. Little, President, ISSCR, to Senators Wendy Askew & Rachel Siewert (July 16, 2021) (on file with Hous. J. Health L. & Pol'y).

[15] Sarah Martin, *Controversial Mitochondrial Donation Legislation Passed After Conscience Vote*, THE GUARDIAN (Dec. 1, 2021), https://www.theguardian.com/australia-news/2021/dec/01/controversial-mitochondrial-donation-legalised-after-conscience-vote; Kimberly Caines, *Maeve's Law: Mitochondrial Disease Bill Pushed to Next Year Could Delay Family Planning*, THE WEST AUSTRALIAN, https://thewest.com.au/politics/federal-politics/maeves-law-mitochondrial-disease-bill-pushed-to-next-year-could-delay-family-planning-c-4803222; *Mitochondrial Donation Law Reform (Maeve's Law) Bill 2021* (Cth) (Austl.), https://www.aph.gov.au/Parliamentary_Business/Bills_LEGislation/Bills_Search_Results/Result?bId=r6697 [hereinafter *Mitochondrial Donation Law Reform (Maeve's Law) Bill 2021*].

[16] *Mitochondrial Donation*, AUSTL. GOV'T DEP'T HEALTH & AGED CARE (Oct. 3, 2022), https://www.health.gov.au/initiatives-and-programs/mitochondrial-donation (noting that Maeve's law was assented to on April 1, 2022).

[17] Myrisha S. Lewis, *How Subterranean Regulation Hinders Innovation in Assisted Reproductive Technology*, 39 CARDOZO L. REV. 1239 (2018); Myrisha S. Lewis, *How Analogizing Socio-Legal Responses to Organ Transplantation Can Further the Legalization of Reproductive Genetic Innovation*, 74 SMU L. REV. 665 (2021).

[18] For more on the benefits of deliberative democracy, *see generally* Nicole Curato et al., *Twelve Key Findings in Deliberative Democracy Research*, 146 DÆDALUS 28 (2017); Melissa De Witte, *Could Deliberative Democracy Depolarize America? Stanford Scholars Think So*, STAN. NEWS (Feb. 4, 2021), https://news.stanford.edu/2021/02/04/deliberative-democracy-depolarize-america/.

[19] While there have been several International Summits on Gene Editing, convened by various bodies, including the National Academies of Sciences, there has been no equivalent "national" summit, convened by any regulatory agency. *See* Part I B-C and II.A-B (discussing

a piecemeal approach to the larger issue of reproductive genetic innovation in the United States and other countries.

Part I of the Article provides brief scientific and bioethical background on mitochondrial transfer. Part II provides regulatory background on assisted reproductive technology and mitochondrial transfer in the United States, United Kingdom, and Australia. Part III identifies and explains which of the regulatory and deliberative mechanisms used in the United Kingdom's and Australia's legalizations of mitochondrial transfer could be adapted for use in the United States. The Article then concludes.

I. MITOCHONDRIAL TRANSFER

Assisted reproductive technology is becoming increasingly prevalent in the U.S. and abroad and enjoys widespread support in the United States.[20] Assisted reproduction, including IVF, is legal and widely available in the United States.[21] There are also forms of assisted reproduction that involve deliberate genetic changes, what I call "reproductive genetic innovation": cytoplasmic transfer, mitochondrial transfer, and germline genome editing. Cytoplasmic transfer was a technique used in the late 1990s to improve fertility outcomes, and germline (heritable) gene editing in human embryos could prevent the inheritance of disease-causing mutations.[22] Reproductive genetic innovation techniques are largely classified as "experimental" by the regulatory system and many observers

the regulation of reproductive genetic innovation).

[20] Carbone & Cahn, *supra* note 4, at 1031–32 (2010) (noting that "support for IVF is widespread—three-quarters of the American public approves of IVF—and the fifteen states that have mandated some form of insurance for fertility services seem to be a random assortment that include Arkansas, California, Connecticut, Hawaii, Illinois, Louisiana, Maryland, Massachusetts, Montana, New Jersey, New York, Ohio, Rhode Island, Texas, and West Virginia." (citations omitted)).

[21] *See, e.g.*, CTRS. FOR DISEASE CONTROL & PREVENTION, ASSISTED REPROD. TECH. SURVEILLANCE—U.S., 2017, MORBIDITY & MORTALITY WEEKLY REP. (2020).

[22] The U.S. Food and Drug Administration, medical establishment, and much of the public view these techniques as "experimental." *See* MEETING #32 TRANSCRIPT, *supra* note 6, at 46, 80; Barritt et al., *supra* note 6, at 433-34.; Park, *supra* note 6.

although some of the techniques have been used by U.S.-based physicians and continue to be researched and used abroad.[23]

While germline genetic modification has been the subject of x "bombshell" news such as Dr. He Jiankui's use of germline gene editing in embryos that led to the birth of three children, mitochondrial transfer does not receive as much media attention these days but remains significant.[24] This Article will focus on the legalization of mitochondrial transfer although the implications of the Article's arguments related to mitochondrial transfer could be applied to reproductive genetic innovation, including cytoplasmic transfer and germline gene editing, more broadly.[25] Section A of this Part provides scientific background on mitochondrial transfer. Section B of this Part provides a brief overview of the ethical controversy that accompanies mitochondrial transfer.

A. Scientific Background

Mitochondrial transfer (also referred to as "mitochondrial donation therapy" or "mitochondrial replacement therapy") is a type of assisted reproductive technology involving the use of in vitro fertilization and the substitution of genetic material.[26] Mitochondrial transfer targets the mitochondria of a cell, which are organelles found in the cytoplasm of the cell.[27] Mitochondria have their own DNA which is generally believed to be inherited solely from the mother.[28]

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[23] *See* discussion *supra* in the Introduction of countries where mitochondrial transfer and techniques involving reproductive genetic innovation, have been provided to parents.

[24] Greely, *supra* note 6, at 115, 140; R. Alta Charo, *Rogues and Regulation of Germline Editing*, 380 N. ENGL. J. MED. 976 (2019).

[25] *See* GEOFF WATTS ET AL., NUFFIELD COUNCIL ON BIOETHICS, NOVEL TECHNIQUES FOR THE PREVENTION OF MITOCHONDRIAL DNA DISORDERS: AN ETHICAL REVIEW 34–36 (Nuffield Council on Bioethics, 2012), https://www.nuffieldbioethics.org/assets/pdfs/Novel_techniques_for_the_prevention_of_mitochondrial_DNA_disorders.pdf; Sharon Begley, *Gene-Editing Discovery Could Point the Way Toward a 'Holy Grail': Cures for Mitochondrial Diseases*, STAT NEWS (July 8, 2020), https://www.statnews.com/2020/07/08/unexpected-email-leads-to-discovery-of-first-genome-editor-for-mitochondria/.

[26] *See, e.g.*, WATTS ET AL., *supra* note 25, at 36, 38.

[27] *Id.*

[28] *See* NAT'L ACAD. SCIS., ENG'G & MED., MITOCHONDRIAL REPLACEMENT TECHNIQUES: ETHICAL, SOCIAL, AND POLICY CONSIDERATIONS xv (2016); WATTS ET AL., *supra* note 25, at 19. *But see*

Mitochondrial DNA is distinct from nuclear DNA.[29] Mitochondria constitute approximately 0.1% of total DNA in the body.[30] Mitochondria are responsible for providing energy to the cell, so mitochondrial mutations can result in symptoms in parts of the body that require high amounts of energy like "the brain, heart, kidneys and major muscle groups."[31] Mitochondrial transfer is largely praised for its ability to target disease-causing mutations.[32] In mitochondrial transfer, doctors replace defective mitochondria with donor mitochondria.[33]

Mitochondrial transfer could be used to improve fertility outcomes, but its greatest medical promise appears to lie in preventing or lessening the incidence of mitochondrial disease.[34] Due to the complexities of mitochondrial inheritance, it is difficult to ascertain the incidence of mitochondrial disease. In the United States, 1 in 5,000 people are affected by genetic mitochondrial disease.[35] In the United Kingdom, estimates show that 1 in 5,000 people are affected by changes, often referred to as "mutations in mitochondrial DNA…[which] … can affect many different tissues and, in its severest form, is fatal in childhood."[36] In Australia, approximately 1 in 200

Shiyu Luo et al., *Biparental Inheritance of Mitochondrial DNA in Humans*, 115 PROCS.NAT'L ACAD. SCIS. 13039, 13039 (2018) (noting "exceptional cases where paternal [mitochondrial DNA] could be passed to the offspring.").

29 *See* NAT'L ACAD. SCIS., ENG'G & MED., *supra* note 28, at xiv-xv.

30 WATTS ET AL., *supra* note 25, at 19.

31 *Id.* at 21.

32 *See id.* at vii, 57-58.

33 For an overview of the different methods of mitochondrial transfer, see Andres Caicedo et al., *Artificial Mitochondria Transfer: Current Challenges, Advances, and Future Applications* 2017 STEM CELLS INT'L 1 (2017), https://www.hindawi.com/journals/sci/2017/7610414/.

34 Alice Park, *A Baby Was Born with DNA From 3 People. Here's How That's Possible*, TIME (April 11, 2019 5:02 PM), https://time.com/5569057/three-parent-baby-dna/; Rob Stein, *Clinic Claims Success in Making Babies With 3 Parents' DNA*, NPR (June 6, 2018, 5:11 AM), https://www.npr.org/sections/health-shots/2018/06/06/615909572/inside-the-ukrainian-clinic-making-3-parent-babies-for-women-who-are-infertile; Testimony of George Daley before Australian Senate Community Affairs Legislation Committee, Fri., Aug. 6, 2021, *Mitochondrial Donation Reform (Maeve's Law) Bill 2021*, at 25-26.

35 *See Mitochondrial Diseases*, CLEVELAND CLINIC, https://my.clevelandclinic.org/health/diseases/15612-mitochondrial-diseases (last visited Feb. 3, 2022).

36 Mary Herbert & Doug Turnbull, *Mitochondrial Donation — Clearing the Final Regulatory Hurdle in the United Kingdom*, 376 NEW ENGL. J. MED. 171, 171 (2017).

women carry "genetic mutation[s] that could potentially lead to mitochondrial disease developing and 1 in 5,000 babies are born with a severely disabling form of mitochondrial disease that can cause death in infancy, childhood or adulthood."[37] In other words, in Australia, approximately 56 children per year are born with a "severe form of [Leigh syndrome or other mitochondrial disease]."[38]

B. Bioethical Background and Definitional Debate

Mitochondrial transfer is accompanied by many ethical, social, and policy considerations which arise in discussions related to the legalization and the safety of the technique, regardless of jurisdiction.[39] In fact, "[a]t the 2014 FDA Cellular, Tissue, and Gene Therapies Advisory Committee meeting, an FDA employee stated that '[t]he FDA recognizes [that there are] moral, ethical, and social policy issues related to genetic modification of eggs and embryos, and that these issues have the potential to affect regulatory decisions'"—although the employee did not explain exactly what the potential effect of these

[37] AUSTRALIAN MITOCHONDRIAL DISEASE FOUNDATION (AMDF), Submission to Senate Community Affairs References Committee, *Science of Mitochondrial Donation and Related Matters*, [Submission no. 26], 9 May 2018, at 2.; SCIENCE & TECHNOLOGY AUSTRALIA (STA), Submission to Senate Community Affairs References Committee, *Science of Mitochondrial Donation and Related Matters*, [Submission no. 18], Mitochondrial Donation Law Reform (Maeve's Law) Bill 2021, at 3.

[38] McPherson, *supra* note 12.

[39] *See, e.g.*, NAT'L ACAD. SCIS., ENG'G & MED., *supra* note 28, at 79–112; AUSTRALIAN GOV'T, NAT'L HEALTH AND MED. RESEARCH, *Mitochondrial Donation Law Reform (Maeve's Law) Bill 2021*, [Submission no. 17], at 7–8 Council ("[Australian Health Ethics Committee] AHEC is the only national body in Australia with statutory responsibilities for providing advice on ethical issues related to health and for developing human research guidelines . . . The passage of Maeve's Law through the Australian Parliament would lead to important work for AHEC to provide ongoing advice on the ethical implementation of mitochondrial donation. This would include undertaking a limited and focused revision of the *Ethical guidelines on the use of assisted reproductive technology in clinical practice and research* to incorporate guidance specifically on the use of mitochondrial donation in Australian clinical practice.").

issues might be.[40] Further, the agency did not convene a meeting to discuss these issues and specifically prohibited such a discussion.[41]

Debates related to mitochondrial transfer are part of a broader controversy over ART.[42] Beyond "traditional" ART like in vitro fertilization, there are conversations in multiple literatures related to how reproductive rights and possibly society may be impacted by gene modifying techniques.[43] Issues in assisted reproductive technology and genetic innovation also implicate the literatures of equality, access, and disability rights.[44]

There is also a larger bioethical debate related to whether children created using forms of assisted reproductive technology would have existed but for the technology and the proper role of parents in

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[40] Transcript of Center for Biologics Evaluation and Research, U.S. Food & Drug Admin., Cellular, Tissue, and Gene Therapies Advisory Committee Meeting #59 (Feb. 25, 2014) [hereinafter Meeting #59 Transcript], at 13, https://wayback.archive-it.org/7993/20170113010701/http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/CellularTissueandGeneTherapiesAdvisoryCo/UCM426293.pdf.

[41] Lewis, *How Subterranean Regulation Hinders Innovation in Assisted Reproductive Technology*, *supra* note 17, at 1273.

[42] *See supra* notes 4-9.

[43] *See, e.g.*, Sonia Suter, *The 'Repugnance' Lens of* Gonzales v. Carhart *and Other Theories of Reproducing Rights: Evaluating Advanced Reproductive Technologies*, 76 GEO. WASH. L. REV. 1514, 1541–48, 1553 (2008); I. Glenn Cohen, *The Constitution and the Rights Not to Procreate*, 60 STAN. L. REV. 1135, 1139–41, 1148-65 (2008); CHRISTINE OVERALL & ARTHUR L. CAPLAN, WHY HAVE CHILDREN? : THE ETHICAL DEBATE 19–33 (2012); Leon Kass, *The Wisdom of Repugnance*, THE NEW REPUBLIC, June 2, 1997, at 24; Leon Kass, *The Wisdom of Repugnance: Why We Should Ban the Cloning of Humans*, 32 VAL. U. L. REV. 679, 704 (1998); *see generally* John A. Robertson, *Genetic Selection of Offspring Characteristics*, 76 B.U. L. REV. 421 (1996) (discussing the ethical and legal implications of a number of technologies, including pre-implantation genetic diagnosis); John A. Robertson, *Embryos, Families, and Procreative Liberty: The Legal Structure of the New Reproduction*, 59 S. CAL. L. REV. 939 (1986) (discussing "[t]he legal structure of the new reproduction").

[44] Suter, *supra* note 43, at 1556–66 (2008); Vence L. Bonham & Lisa E. Smilan, *Somatic Genome Editing in Sickle Cell Disease: Rewriting a More Just Future*, 97 N.C. L. REV. 1093, 1136–43 (2019); NATURE BIOTECHNOLOGY, CRISPR GERMLINE ENGINEERING—THE COMMUNITY SPEAKS, 33 NATURE BIOTECH. 478, 481 (2015) ("in some instances, [like] correction of hearing deficits or enhancement of stature—patient groups have argued that the 'defect' is a perfectly acceptable form of human variation that should not be subjected to genetic cleansing."); Courtney Megan Cahill, *Obergefell and the "New" Reproduction*, 100 MINN. L. REV. HEADNOTES 1, 1, 11 (2016); Seema Mohapatra, *Assisted Reproduction Inequality and Marriage Equality*, 92 CHI. KENT L. REV. 87, 88, 91-97 (2017).

selecting traits for children via assisted reproductive technology.[45] Bioethicists and sociologists have substantially analyzed the impacts of assisted reproductive technology and genetic modification on identity.[46] Issues related to identity accompany advanced assisted reproductive technologies as bioethicists and the public ask whether these techniques impact the identity of the children conceived using these technologies. For many bioethicists, modifications of non-nuclear DNA are not viewed as modifying "identity."[47] Similarly, there are concerns about parents' ability to impact not only their children, but future generations of children.[48] This leads to arguments based on hubris, sometimes from religious perspectives, in which observers note that physicians are "playing God" and will lead society down a "slippery slope" through actions involving genetic

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[45] *See, e.g.*, DOV FOX, BIRTH RIGHTS AND WRONGS: HOW MEDICINE AND TECHNOLOGY ARE REMAKING REPRODUCTION AND THE LAW 145 (2019) (citation omitted).

[46] *See* sources cited *supra* note 34; *see also* Karinne Ludlow, *Genetic Identity Concerns of Novel Reproductive Techniques*, J.L. & BIOSCI. 1, 2–3.

[47] *See* Shoukhrat Mitalipov & Don P. Wolf, *Clinical and Ethical Implications of Mitochondrial Gene Transfer*, 25 TRENDS ENDOCRINOL. METAB. 5, 7 (2014); Rob Stein, *Her Son Is One of the Few Children to Have 3 Parents' DNA*, NPR (June 6, 2018, 5:47 PM), https://www.npr.org/sections/health shots/2018/06/06/616334508/her-son-is-one-of-the-few-children-to-have-3-parents. For sources supporting the idea that mitochondrial replacement therapy does not affect identity; *see* HUM. FERTILISATION & EMBRYOLOGY AUTH., MITOCHONDRIA REPLACEMENT CONSULTATION: ADVICE TO GOVERNMENT 21 (2013), https://www.hfea.gov.uk/media/2618/mitochondria_replacement_consultation_-_advice_for_government.pdf [hereinafter ADVICE TO GOVERNMENT]; *see* Jackie Leach Scully, *A Mitochondrial Story: Mitochondrial Replacement, Identity and Narrative*, 31 BIOETHICS 37, 39 (2017) (noting that "social processes . . . form and maintain identity"); *see generally* Alexandra Reznichenko et al., *Mitochondrial Transfer: Ethical, Legal and Social Implications in Assisted Reproduction*, 8 S. AFR. J. BIOETHICS & L. 32, 33–34 (2015) ("Other kinship forms that challenge the argument of loss of identity in children with 'three' parents include adoption, surrogacy and use of donor gametes (sperm or oocytes alike) or gestational carriers."); *see* Rosamund Scott & Stephen Wilkinson, *Germline Genetic Modification and Identity: The Mitochondrial and Nuclear Genomes*, 37 OXFORD J. LEGAL STUD. 886, 914 (2017) (discussing the impacts of mitochondrial replacement therapies and nuclear genome editing on identity and offering arguments on both sides of the identity alteration debate). *But see* A. L. Bredenoord et al., *Ethics of Modifying the Mitochondrial Genome*, 37 J. MED. ETHICS 97, 98–99 (2011); Calum MacKellar, *Genome Modifying Reproductive Procedures and Their Effects on Numerical Identity*, 25 NEW BIOETHICS 121, 131 (2019).

[48] Sarah Polcz & Anna Lewis, *CRISPR-CAS9 and the Non-Germline Non-Controversy*, 3 J.L. & BIOSCI. 413, 415 (2016); Sonia M. Suter, *A Brave New World of Designer Babies?*, 22 BERKELEY TECH. L.J. 897, 963 (2007).

modification which constitute a "step too far."[49] Others, including religious groups, note that mitochondrial transfer and techniques that can lead to the disposal of embryos "do not respect the human dignity of embryos."[50] In previous works, I have argued that in spite of these ethical objections, advanced assisted reproductive technologies ("AARTs") and germline gene editing should be treated similarly to ART and thus regulated by states and not the federal government.[51]

Concerns over genetic modification are often heightened when changes affect the "germline," meaning that the changes are inheritable by subsequent offspring. For example, the fact that mitochondrial transfer made a change "at" the germline was the basis for mitochondrial transfer's prior illegality in the United Kingdom.[52]

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[49] *See* Clyde Haberman, *Scientists Can Design 'Better' Babies. Should They?*, N.Y. TIMES (June 10, 2018), https://www.nytimes.com/2018/06/10/us/11retro-baby-genetics.html; David Warmflash, *Religious Beliefs Shape Our Thinking on Cloning, Stem Cells, and Gene Editing*, GENETIC LITERACY PROJECT (Nov. 27, 2019), https://geneticliteracyproject.org/2019/11/27/religious-beliefs-shape-our-thinking-on-cloning-stem-cells-and-gene-editing/; Rob Stein, *House Committee Votes to Continue Ban On Genetically Modified Babies*, NPR (Jun. 4, 2019, 4:38 PM) https://www.npr.org/sections/health-shots/2019/06/04/729606539/house-committee-votes-to-continue-research-ban-on-genetically-modified-babies; Agneta Sutton, *A Case Against Germ-Line Gene Therapy*, 29 ETHICS & MED. 17, 20–22 (2013); James J. Walter, *Theological Issues in Genetics*, 60 THEOLOGICAL STUD. 124, 129–132 (1999); Marc A. Thiessen, *Gene Editing Is Here. It's an Enormous Threat.*, WASH. POST (Nov. 29, 2018), https://www.washingtonpost.com/opinions/gene-editing-is-here-its-an-enormous-threat/2018/11/29/78190c96-f401-11e8-bc79-68604ed88993_story.html; Michael J. Sandel, *The Case Against Perfection*, THE ATLANTIC (Apr. 2004), https://www.theatlantic.com/magazine/archive/2004/04/the-case-against-perfection/302927/; Chi C. Wong & Martin H. Johnson, *Therapy for Mitochondrial Genetic Disease: Are We at the Thin End of the Wedge?*, 29 REPROD. BIOMED. ONLINE 147, 148 (2014); William Gardner, *Can Human Genetic Enhancement Be Prohibited?*, 20 J. MED. & PHIL. 65, 65–67 (1995); Erik Parens, *Should We Hold the (Germ) Line?*, 23 J.L. MED. & ETHICS 173, 174, 176 (1995); Marcy Darnovsky, *A Slippery Slope to Human Germline Modification,* 499 NATURE 127, 127 (2013); Tony McGleenan, *Human Gene Therapy and Slippery Slope Arguments*, 21 J. MED. ETHICS 350, 350 (1995); NAT'L ACAD. SCIS., ENG'G & MED., *supra* note 28, at 7. *But see* Kenan Malik, Opinion, *The Three-Parent Baby's First Step*, N.Y. TIMES (Feb. 22, 2015), http://www.nytimes.com/2015/02/23/opinion/the-three-parent-babys-first-step.html.

[50] THE SENATE CMTY. AFFS. LEGIS. COMM., *Mitochondrial Donation Law Reform (Maeve's Law) Bill 2021 [Provisions]*, Aug. 2021, at 31 [hereinafter *Maeve's Law Provisions*].

[51] *See, e.g.*, Lewis, *How Subterranean Regulation Hinders Innovation in Assisted Reproductive Technology*, *supra* note 17, at 1259-262; Myrisha S. Lewis, *Is Germline Gene Editing Exceptional?*, 51 SETON HALL L. REV. 735 (2020).

[52] For an analysis of U.K. law's distinctions between "germline modification," "germline genetic modification," and "genetic modification," ultimately culminating in the legal permissibility of mitochondrial transfer procedures, *see* Scott & Wilkinson, *supra* note 47, at 886–87, 891, 897–

The use of techniques involving heritable genetic modifications in the United States are stymied by the recent recurring budget rider.[53]

Some argue that all uses of mitochondrial transfer constitute a change to the human germline. whereasOthers argue that because mitochondria are maternally inherited, only the use of modified female embryos constitutes a human germline modification.[54] Some note that techniques like mitochondrial transfer involve a germline modification but not in the same way as germline gene editing as those AARTs involve the modification of non-nuclear DNA, which differentiates them from germline gene editing.[55] Others argue that mitochondrial DNA are insignificant and thus not part of a germline modification.[56] Some even contest the idea that mitochondrial transfer is "genetic manipulation" at all.[57]

An Institute of Medicine panel, convened to study mitochondrial replacement techniques at the FDA's request, concluded that mitochondrial replacement is not heritable genetic modification.[58] This conclusion partly rested on the widely-accepted belief that mitochondria are maternally transmitted; for this reason, the National

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53 *See discussion* in Part II *infra.*

54 *See* Scott & Wilkinson, *supra* note 47 (referencing NAT'L ACAD. OF SCIS., ENG'G & MED., MITOCHONDRIAL REPLACEMENT TECHNIQUES (2016)).

55 *See* Viswanathan, *supra* note 11(quoting Eli Adashi, M.D.: "[Mitochondrial replacement therapy] can technically be construed as germline modification, so mitochondrial replacement got swept up into that [Congressional budget] rider. It was caught up in the gene editing concerns, and I think it's sort of an unfortunate linkage."); Eli Y. Adashi & I. Glenn Cohen, *Going Germline: Mitochondrial Replacement as a Guide to Genome Editing*, 164 CELL 832, 833 (2016).

56 Ainsley J. Newson & Anthony Wrigley, *Is Mitochondrial Donation Germ-Line Gene Therapy? Classifications and Ethical Implications*, 31 BIOETHICS 55, 58 (2017) (citing PUBLIC HEALTH DIRECTORATE/HEALTH SCIENCE AND BIOETHICS DIVISION, MITOCHONDRIAL DONATION: A CONSULTATION ON DRAFT REGULATIONS TO PERMIT THE USE OF NEW TREATMENT TECHNIQUES TO PREVENT THE TRANSMISSION OF A SERIOUS MITOCHONDRIAL DISEASE FROM MOTHER TO CHILD (2014) and observing "[t]he implication here being that if a change is not significant, it does not constitute gene therapy (of any kind).").

57 *Emerging Mitochondrial Therapies and Their Ethicality,* HARV. SCI. REV. (Dec. 09, 2018), https://harvardsciencereview.org/2018/12/09/emerging-mitochondrial-therapies-and-their-ethicality/.

58 NAT'L ACAD. SCIS., ENG'G & MED., *supra* note 28, at 88 ("This committee . . . views 'genetic modification' and 'germline modification' as two separate concepts, the first being 'changes to the genetic material within a cell' and the latter 'human inheritable genetic modification.'").

Academies of Sciences recommended that only male embryos be initially selected if mitochondrial transfer was used in the United States.[59] The ISSCR also maintains that there is a difference between mitochondrial replacement therapy (MRT) and heritable genome editing and that MRT research and clinical use should be permissible.[60] The ISSCR's position does not include a sex-based caveat or recommendation.[61] The next Part details regulatory responses in the U.S., U.K., and Australia to the bioethical considerations that accompany MRT.

II. Regulation of ART and Mitochondrial Transfer in the United States, United Kingdom, and Australia

The similarities between the U.S., U.K., and Australia render the potential lessons from those countries applicable to the United States. First, as alluded to in the Article's title, all three are classified as "common law countries."[62] Second, while the U.K. and Australia are most similar, all three countries' governments contain federal structures.[63] Third, in vitro fertilization is legal in all three counties, albeit under differing regulatory regimes.[64] Fourth, each country was an early user of in vitro fertilization; the first babies born in the United

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[59] *See id.* at xv. *But see* Luo et al., *supra* note 28, at 13939 (noting "exceptional cases where paternal [mitochondrial DNA] could be passed to the offspring.").

[60] *Maeve's Law Provisions*, *supra* note 50, at 39.

[61] *Id.*

[62] *Foreign Legal Research Guide*, PRITZKER LEG. RSCH. CTR., https://library.law.northwestern.edu/Foreign/legalsystems (last visited Dec. 14, 2021) ("Examples of common law countries include the United States, Australia, and the United Kingdom (except for Scotland, Guernsey, and Jersey)."); *The Common Law and Civil Law Traditions*, BERKELEY LAW: THE ROBBINS COLLECTION 1, 5, https://www.law.berkeley.edu/research/the-robbins-collection/exhibitions/common-law-civil-law-traditions/.

[63] Steven G. Calabresi, *Does Institutional Design Make A Difference?*, 109 NW. U. L. REV. 577, 582–83 (2015).

[64] The U.K. and Australia have centralized regimes for accessing in vitro fertilization, whereas the United States has been categorized as "the Wild Wild West." *See* Alexander N. Hecht, *The Wild Wild West: Inadequate Regulation of Assisted Reproductive Technology*, 1 HOUS. J. HEALTH L. & POL'Y 227, 228 (2001).

Kingdom (and the world), Australia, and the United States as a result of IVF, were born in 1978, 1980, and 1981, respectively.[65]

In the American legal literature, analysis of assisted reproductive technology tends to focus on the lack of regulation of assisted reproductive technology in the U.S. and how this lack of regulation stands in stark contrast to the U.K.'s robust system for ART regulation through the Human Fertilisation & Embryology Authority.[66] Similarly, accounts in multiple literatures focus on the first child born as a result of in vitro fertilization, Louise Brown, in July 1978 in the United Kingdom, along with the publication of the results of the Warnock Committee's report.[67] The Warnock Committee Report shows that public consideration of the moral, ethical, and social issues have existed since the early days of IVF in the U.K.[68] Yet, these accounts often leave out innovations in Australia. For example, Australia funded IVF research "and by 1984, the team at Monash University in Melbourne had overtaken the UK as the world-leader with a series of other firsts, including twins, triplets, babies born from donor eggs and

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[65] *See The American Experience*, PBS, https://www.pbs.org/wgbh/americanexperience/features/babies-americas-first/; Elizabeth Simpson, *America's 1st test-tube baby, a Norfolk native, set to meet world's 1st test-tube baby* (Mar. 3, 2017, 6:00 PM), https://www.pilotonline.com/news/health/article_17303144-c2b8-55e2-8669-11d42d894fc6.html; *History, Timeline*, MONASH IVF, https://monashivf.com/why-monash-ivf/history/; https://www.marieclaire.com.au/candice-thum-australia-first-ivf-baby-birthday.

[66] Ellen S. Fischer, *The 'Wild West' of Medicine: An Argument for Adopting the United Kingdom's 'HFEA' Framework, to Improve the Market for Assisted Reproduction in the United States*, 39 NW. J. INT'L L. & BUS. 201, 203–04, 217 (2019); Alicia Ouellette et al., *Lessons Across the Pond: Assisted Reproductive Technology in the United Kingdom and the United States*, 31 B.U. AM. J. L. & MED. 419, 419, 423, 430, 434–35 (2005).

[67] *See* DEP'T HEALTH & SOC. SEC., REPORT OF THE COMMITTEE OF INQUIRY INTO HUMAN FERTILISATION & EMBRYOLOGY, 1984, HC 9314 (UK), https://www.hfea.gov.uk/media/2608/warnock-report-of-the-committee-of-inquiry-into-human-fertilisation-and-embryology-1984.pdf; Natasha Hammond-Browning, *Ethics, Embryos, and Evidence: A Look Back at Warnock*, 23 OXFORD MED. L. REV. 588, 588–619 (2015); Katharine Dow, *'The Men Who Made The Breakthrough': How the British Press Represented Patrick Steptoe and Robert Edwards in 1978*, 4 REPROD. BIOMED. & SOC'Y ONLINE 59, 59–67 (2017); Jody Schechter, *Promoting Human Embryonic Stem Cell Research: A Comparison of Policies in the United States and the United Kingdom and Factors Encouraging Advancement*, 45 TEX. INT'L L.J. 603, 614–16 (2010); Margaret Foster Riley & Richard A. Merrill, *Regulating Reproductive Genetics: A Review of American Bioethics Commissions and Comparison to the British Human Fertilisation and Embryology Authority*, 6 COLUM. SCI. & TECH. L. REV. 1, 103, 105, 110–114 (2001).

[68] *See* DEP'T HEALTH & SOC. SEC., *supra* note 67.

frozen embryos."[69] Today, the U.K. has arguably regained its position as the world leader in ART with its legalization of mitochondrial transfer. Australia is following as it lays the groundwork for the potential clinical use of mitochondrial transfer, while the United States remains in a regulatory standstill, despite the progress made in the U.S. related to the underlying science of mitochondrial transfer.[70]

A. United States

Although the practice of medicine is mostly regulated by the states, the FDA has blocked the use of mitochondrial transfer and other related techniques by asserting jurisdiction over them.[71] Over the past 20 years, the federal legal system discouraged the use of mitochondrial transfer in the United States as evidenced by the issuance of Untitled Letters to physician-researchers engaged in both mitochondrial

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[69] Michael Morrison & Stevienna de Saille, *CRISPR in Context: Towards a Socially Responsible Debate on Embryo Editing*, PALGRAVE COMMC'NS (Sept. 2019), at 4 (citing Harry Kannegiesser, CONCEPTION IN THE TEST TUBE: THE IVF STORY: HOW AUSTRALIA LEADS THE WORLD (Macmillan Australia 1988)).

[70] *See* Viswanathan, *supra* note 11; *see, e.g.*, Ariana Eunjung Cha, *This Fertility Doctor is Pushing the Boundaries of Human Reproduction, with Little Regulation*, WASH. POST: HEALTH & SCI. (May 14, 2018, 7:00 AM), https://www.washingtonpost.com/national/health-science/this-fertility-doctor-is-pushing-the-boundaries-of-human-reproduction-with-little-regulation/2018/05/11/ea9105dc-1831-11e8-8b08-027a6ccb38eb_story.html; Jill Neimark, *A Baby with 3 Genetic Parents Seems Healthy, but Questions Remain*, NPR: TREATMENTS (Apr. 8, 2017, 5:00 AM), https://www.npr.org/sections/health-shots/2017/04/08/523020895/a-baby-with-3-genetic-parents-seems-healthy-but-questions-remain; Michelle Roberts, *First 'Three Person Baby' Born Using New Method*, BBC NEWS (Sept. 27, 2016), https://www.bbc.com/news/health-37485263; Robinson, *supra* note 7; Giselle Lee, *Shoukhrat Mitalipov and Masahito Tachibana's Mitochondrial Gene Replacement Therapy Technique*, THE EMBRYO PROJECT ENCYCLOPEDIA (Sept. 6, 2017), https://embryo.asu.edu/pages/shoukhrat-mitalipov-and-masahito-tachibanas-mitochondrial-gene-replacement-therapy-technique.

[71] *See Therapeutic Cloning and Genome Modification, Cellular & Gene Therapy Products*, U.S. FOOD & DRUG ADMIN. (Mar. 16, 2018), https://www.fda.gov/biologicsbloodvaccines/cellulargenetherapyproducts/ucm2007205.htm ("In March 2001, FDA sent a letter to the research community asserting regulatory authority over clinical research using cloning technology to create a human being, and to advise that FDA regulatory process is required in order to initiate these investigations. FDA jurisdiction includes human cells used in therapy involving the transfer of genetic material by means other than the union of gamete nuclei. Examples of such genetic material include, but are not limited to: cell nuclei (for cloning), oocyte nuclei, ooplasm, which contains mitochondria and genetic material contained in a genetic vector, transferred to gametes or other cells. Any clinical research involving these techniques would require an IND.").

transfer and techniques similar to mitochondrial transfer.[72] These FDA-issued Untitled Letters and "advisories" fall short of official enforcement actions but nonetheless discourage physicians and scientists from using and researching techniques involving reproductive genetic innovation and also human reproductive cloning, an idea that generated an extensive uproar in the 1990s and early 2000s.[73]

The FDA has posted an advisory online, listing the techniques that it proclaims require an investigational new drug (IND) application even though these techniques involve the practice of medicine, which is regulated by states and not the federal government.[74] The FDA's online advisory applies to a number of techniques, including mitochondrial transfer, germline gene editing, and cytoplasmic transfer.[75]

In 2015, approximately five years into the FDA's subterranean regulation of techniques involving reproductive genetic innovation, Congress added an appropriations rider to the 2016 budget to prevent the FDA from using funds on the aforementioned IND applications involving heritable genetic modification.[76] The rider, which was accompanied by little substantive discussion in Congress, reads:

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[72] For a general overview of the FDA's pattern of using guidance documents (including online advisories) and Untitled Letters, *see generally* sources cited, *supra* note 17; *see also Issues Raised by Human Cloning Research: Hearing Before the H. Subcomm. on Oversight and Investigations of the Comm. on Energy and Commerce*, 107th Cong. 78–81 (2001) (providing the statement of Kathryn C. Zoon, Dir. of Ctr. for Biologics Evaluation & Research, U.S. Food & Drug Admin.); Stuart L. Nightingale, *Letter About Human Cloning*, U.S. FOOD & DRUG ADMIN. (Oct. 26, 1998), http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm150508.htm.

[73] *See supra* note 72 and accompanying text.

[74] *See FDA Regulation of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/P's) Product List*, U.S. FOOD & DRUG ADMIN. (Feb. 1, 2018), https://www.fda.gov/vaccines-blood-biologics/tissue-tissue-products/fda-regulation-human-cells-tissues-and-cellular-and-tissue-based-products-hctps-product-list [https://perma.cc/B3HK-BBW3] [hereinafter *Product List*]. In prior works, I have argued that the FDA's declaration exceeded its jurisdiction. *See generally* sources cited, *supra* note 17; Myrisha S. Lewis, *Innovating Federalism in the Life Sciences*, 92 TEMPLE L. REV. 383, 391–402 (2020) (discussing the practice-products divide in medical innovation).

[75] *See Product List*, *supra* note 74.

[76] Russell A. Spivak et al., *Germ-line Gene Editing and Congressional Reaction in Context: Learning from Almost 50 Years of Congressional Reactions to Biomedical Breakthroughs*, 30 J.L. & HEALTH 20, 21–22 (2017); Consolidated Appropriations Act of 2016, Pub. L. No. 114-113, § 749, 129 Stat. 2283, 2283 (2015).

> None of the funds made available by this Act may be used to notify a sponsor or otherwise acknowledge receipt of a submission for an exemption for investigational use of a drug or biological product under section 505(i) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(i)) or section 351(a)(3) of the Public Health Service Act (42 U.S.C. 262(a)(3)) in research in which a human embryo is intentionally created or modified to include a heritable genetic modification. Any such submission shall be deemed to have not been received by the Secretary, and the exemption may not go into effect.[77]

That rider has been renewed every subsequent year.[78] Thus, even though both the FDA's informal regulation and Congress' recent recurring budget rider have both been unaccompanied by substantial legal explanation, it is likely that public deliberation will be necessary to change the regulatory treatment of mitochondrial transfer.

This regulatory treatment has not prevented some U.S.-based physicians from traveling abroad to provide the technique to patients in countries with more favorable regulatory climates.[79] For example, the U.S.-based physician, Dr. John Zhang traveled to Mexico to

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[77] Consolidated Appropriations Act of 2016, H.R. 2029, 114th Cong. (2015) [hereinafter CAA] (prohibiting the FDA from consider applications involving "heritable genetic modification."). While the budget rider focuses on a clinical investigation and the domestic creation of a "genetically modified embryo," neither the budget rider nor the FDA's letter to Dr. John Zhang addresses the potential role of foreign clinical trials in support of a BLA or IND application. *See* Letter from Mary A. Malarkey, Dir., Off. of Compliance & Biologics Quality, Trustee for Biologics Evaluation & Rsch., to John Zhang, Chief Exec. Officer, Darwin Life, Inc. & New Hope Fertility Ctr., FDA (Aug. 4, 2017) [hereinafter Letter from Mary A. Malarkey], https://www.fda.gov/media/106739/download [https://perma.cc/5PEC-8RZP]; U.S. FOOD & DRUG ADMIN., *Guidance for Industry and FDA Staff: FDA Acceptance of Foreign Clinical Studies Not Conducted Under an IND: Frequently Asked Questions* (March 2012), https://www.fda.gov/files/about%20fda/published/FDA-Acceptance-of-Foreign-Clinical-Studies-Not-Conducted-Under-an-IND—Frequently-Asked-Questions.pdf; Anna M. O'Connell et al., *Global Approaches to Drug Development: When Ex-US Clinical Data Can Support US Drug Approvals*, IQVIA, https://www.iqvia.com/-/media/iqvia/pdfs/library/white-papers/global-approaches-to-drug-development.pdf (last visited Nov. 16, 2021); 21 C.F.R. § 314.106 (2022).

[78] Spivak et al., *supra* note 76, at 21-22; *see* CAA, *supra* note 77 (rider text and accompanying text).

[79] *See*, *e.g.*, Roberts, *supra* note 70.

provide the technique to a couple who wanted to avoid transmitting Leigh's syndrome to their children.[80] Providing the technique in Mexico allowed Dr. Zhang, his team, and the intended parents to avoid the limitations of the U.S. regulatory system.[81] After providing mitochondrial transfer in Mexico and requesting a pre-IND meeting with the FDA, Dr. John Zhang was informed by letter that the FDA could not consider its application due to the congressional budget rider.[82]

Dr. Shoukhrat Mitalipov of the Oregon Health Sciences University has achieved mitochondrial transfer in rhesus macaques; however, the use of this techniques in human pregnancies has not yet occurred.[83] In 2015, Mitalipov confirmed that he had submitted two applications to the FDA for clinical trials related to mitochondrial transfer.[84] While Dr. Mitalipov predicted a potential year-long delay by the FDA in order to

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[80] *See, e.g.*, *id.*; Ariana Eunjung Cha, *This Fertility Doctor is Pushing the Boundaries of Human Reproduction, with Little Regulation*, WASH. POST (May 14, 2018, 7:00 AM), https://www.washingtonpost.com/national/health-science/this-fertility-doctor-is-pushing-the-boundaries-of-human-reproduction-with-little-regulation/2018/05/11/ea9105dc-1831-11e8-8b08-027a6ccb38eb_story.html; Neimark, *supra* note 70.

[81] *See, e.g.*, Neimark, *supra* note 70. *See* Jessica Hamzelou, *Exclusive: World's First Baby Born with New "3 Parent" Technique*, NEW SCIENTIST (Sept. 27, 2016), https://www.newscientist.com/article/2107219-exclusive-worlds-first-baby-born-with-new-3-parent-technique/ ("Neither [mitochondrial transfer] method has been approved in the US, so Zhang went to Mexico instead, where he says 'there are no rules.'"). While this Article focuses on strides in mitochondrial DNA research as applied to reproductive genetic innovation, research in mitochondrial DNA outside of reproduction continues. *See, e.g.*, UCLA HEALTH SCIS., *Scientists Develop High-Throughput Mitochondria Transfer Device*, SCI. DAILY (Dec. 29, 2020), https://www.sciencedaily.com/releases/2020/12/201229140838.htm.

[82] *See* Letter from Mary A. Malarkey, *supra* note 77, at 1.

[83] *See* Robinson, *supra* note 7; Lee, *supra* note 70.

[84] Steve Connor, *Scientist Who Pioneered 'Three-Parent' IVF Embryo Technique Now Wants to Offer it to Older Women Trying for a Baby*, THE INDEPENDENT (Feb. 8, 2015, https://www.independent.co.uk/news/science/threeparent-embryos-an-ivf-revolution-or-a-slippery-slope-to-designer-babies-10031477.html ("Professor Mitalipov, who has advised Britain's Human Fertilisation and Embryology Authority (HFEA) on mitochondrial transfer, confirmed he has applied to the FDA for two clinical trials licences, one for treating mitochondrial disease, the other for treating age-related infertility. 'It's all one package,' he said. 'We use the same treatment for mitochondrial disease patients, and, separately, another trial will be for women of advanced age.' 'They may approve one procedure first and then a second. That's my expectation,' he said. 'So far we haven't heard anything from the FDA on the specifics of how they want us to run this clinical trial. My sense is that they want to take the route that the HFEA did. 'They want to maybe look first into ethics,' he added. 'I think we're talking of another year of delay.'").

consider ethical issues related to mitochondrial transfer, the recent trajectory of U.S. restrictions means that predicted year-long delay is continuing to grow.[85] For example, as indicated by the FDA's 2017 letter to Dr. John Zhang, in spite of objections by many scientists, the FDA has interpreted a recuring Congressional budget rider preventing the agency from using funds on applications involving "heritable genetic modification" to encompass mitochondrial transfer, thus stymying innovation related to mitochondrial transfer in the U.S.[86] Moral views have shaped legislation and regulatory decisions and will continue to do so.[87] Currently, concerns about embryo destruction, "playing God," possibly harming future children using germline gene editing, the possibility of using enhancement for gene editing, and the idea of changing the gene pool have been proffered as possible rationales underlying the current budget rider prohibiting FDA-consideration of IND applications involving heritable genetic modification in the United States.[88]

B. United Kingdom

The United Kingdom has played an important role in the development of assisted reproductive technology. The first child in the world born as a result of in vitro fertilization, Louise Brown, was born in the U.K.[89] The Human Fertilisation & Embryology Authority (HFEA) "is the UK's independent regulator of treatment using eggs and sperm, and of treatment and research involving human

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[85] *Id.*

[86] *See* Letter from Mary A. Malarkey, *supra* note 77, at 1; Spivak et al., *supra* note 76, at 21-22; Consolidated Appropriations Act of 2016, Pub. L. No. 114-113, § 749, 129 Stat. 2283, 2283 (2015) (prohibiting the FDA from considering applications involving heritable genetic modification).

[87] Seema Mohapatra, *Politically Correct Eugenics*, 12 FIU L. REV. 51, 54 (2016) (noting "the effect of eugenic ideals in the legislative policies of the United States" including immigration and anti-miscegenation laws).

[88] I. Glenn Cohen, *Circumvention Medical Tourism and Cutting-Edge Medicine: The Case of Mitochondrial Replacement Therapy*, 25 IND. J. GLOB. LEGAL STUD. 439, 453–54 (2018) (noting the scant legislative history accompanying the budget rider which prohibits FDA consideration of techniques involving heritable genetic modification); Stein, *supra* note 49.

[89] Press Release, The Nobel Assembly at Karolinska Institute, The Nobel Prize in Physiology or Medicine 2010 (Oct. 4, 2010), https://www.nobelprize.org/prizes/medicine/2010/press-release/ [https://perma.cc/CK2M-NNJE].

embryos."[90] As such, the HFEA is responsible for a number of tasks including licensing individual fertility clinics and research centers and "…regulat[ing] the storage of gametes and embryos…"[91] As of the HFEA's last annual report, released in November 2021, 103 clinics were licensed by the HFEA to provide fertility treatment.[92] Sixteen additional licenses permitted research involving human embryos and fourteen additional licenses provided for storage of gametes and embryos only.[93] In addition to licensing, the HFEA also publishes guidelines for fertility providers.[94]

After a lengthy legalization process that included multiple public consultations, multiple scientific reviews, and extensive scientific and bioethical support, the UK legalized mitochondrial transfer in 2015.[95]

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[90] *About Us*, HUMAN FERTILISATION & EMBRYOLOGY AUTH., https://www.hfea.gov.uk/about-us.

[91] *See Annual Report and Accounts 2012/13*, HUMAN FERTILISATION & EMBRYOLOGY AUTH., 1, 8–9 (2013), https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/246699/0323.pdf [hereinafter 2013 ANNUAL REPORT]; Human Fertilisation and Embryology Act, 1990, c. 37, §§ 5-10 (Eng.); Steve P. Calandrillo & Chryssa V. Deliganis, *In Vitro Fertilization and the Law: How Legal and Regulatory Neglect Compromised A Medical Breakthrough*, 57 ARIZ. L. REV. 311, 333 (2015); *About Us*, *supra* note 90; HUM. FERTILISATION & EMBRYOLOGY AUTH., *supra* note 10.

[92] *State of the Fertility Sector 2020/2021,* HUM. FERTILISATION & EMBRYOLOGY AUTH. (Nov. 2021), http://www.hfea.gov.uk/about-us/publications/research-and-data/state-of-the-fertility-sector-2020-2021/.

[93] *Id.*; *Applying for a Clinic License*, HUM. FERTILISATION & EMBRYOLOGY AUTH., https://www.hfea.gov.uk/about-us/applying-for-a-clinic-licence/.

[94] HUM. FERTILISATION & EMBRYOLOGY AUTH., CODE OF PRACTICE 11 (9th ed. 2019), https://www.hfea.gov.uk/media/2793/2019-01-03-code-of-practice-9th-edition-v2.pdf.

[95] *See* Shoot, *supra* note 5. For the "three scientific reviews" of mitochondrial transfer (and the 2014 addendum to the "further update in 2014"), *see generally* HUM. FERTILISATION & EMBRYOLOGY AUTH., ANNEX VIII: SCIENTIFIC REVIEW OF THE SAFETY AND EFFICACY OF METHODS TO AVOID MITOCHONDRIAL DISEASE THROUGH ASSISTED CONCEPTION: UPDATE (2013), https://www.hfea.gov.uk/media/2612/mito-annex_viii-science_review_update.pdf; HUM. FERTILISATION & EMBRYOLOGY AUTH., REVIEW OF THE SAFETY AND EFFICACY OF POLAR BODY TRANSFER TO AVOID MITOCHONDRIAL DISEASE ADDENDUM TO 'THIRD SCIENTIFIC REVIEW OF THE SAFETY AND EFFICACY OF METHODS TO AVOID MITOCHONDRIAL DISEASE THROUGH ASSISTED CONCEPTION: 2014 UPDATE' (2014), https://www.hfea.gov.uk/media/2610/2014-10-07_-_polar_body_transfer_review_-_final.pdf; HUM. FERTILISATION & EMBRYOLOGY AUTH., SCIENTIFIC REVIEW OF THE SAFETY AND EFFICACY OF METHODS TO AVOID MITOCHONDRIAL DISEASE THROUGH ASSISTED CONCEPTION (2011), https://www.hfea.gov.uk/media/2613/scientific-review-of-the-safety-and-efficacy-of-methods-to-avoid-mitochondrial-disease-through-assisted-conception.pdf; HUM.FERTILISATION & EMBRYOLOGY AUTH., THIRD SCIENTIFIC REVIEW OF THE SAFETY AND

In the United Kingdom, an HFEA-issued license to provide the technique is required and the technique is limited to disease causing mutations.[96] Only two mitochondrial transfer techniques are permitted in the U.K.: maternal spindle transfer and pronuclear transfer.[97] In addition to licensing, the HFEA also approves the individual patients who would receive mitochondrial donation therapy. [98] Currently, the Newcastle Fertility Centre at Life has the sole license for research and treatment of patients using approved mitochondrial donation techniques in the U.K.[99] In 2018, the HFEA approved the Newcastle Fertility Centre's use of mitochondrial donation for two women.[100] So far, no live births have been reported.[101]

C. Australia

In July 1978, when Robert Edwards and Patrick Steptoe announced the birth of Louise Brown, the first baby born as a result of using IVF, researchers in Melbourne were "devastated" to have not achieved this milestone first.[102] Instead, the first baby born as a result

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EFFICACY OF METHODS TO AVOID MITOCHONDRIAL DISEASE THROUGH ASSISTED CONCEPTION: 2014 UPDATE, at 4, 12 (2014), https://www.hfea.gov.uk/media/2614/third_mitochondrial_replacement_scientific_review.pdf; *Parliament Should Approve Regulations for Mitochondrial Donation*, THE GUARDIAN (Jan. 30, 2015), https://www.theguardian.com/science/2015/jan/30/parliament-should-approve-regulations-for-mitochondrial-donation.

[96] *See* HUM. FERTILISATION & EMBRYOLOGY AUTH., *supra* note 10 ("[Anyone] considering mitochondrial donation treatment . . . should consult Newcastle Fertility Centre at Life . . .. If they think you are eligible for treatment, they need to apply to [the Human Fertilization & Embryology Authority] for permission [for treatment]. This is because [the Authority] need[s] to approve every case of mitochondrial donation treatment to make sure it's only done in a legal and ethical way"); *About Us*, *supra* note 90; *see infra* discussion in Part III.

[97] HUM. FERTILISATION & EMBRYOLOGY AUTH., *supra* note 10.

[98] *Id.*

[99] *Id.*

[100] *Doctors Given Approval for UK's First 'Three-Person Babies'*, BBC (Feb. 2, 2018), https://www.bbc.com/news/health-42918341.

[101] *See, e.g.*, I. Glenn Cohen et al., *The Regulation of Mitochondrial Replacement Techniques Around the World*, 21 ANN. REV. GENOMICS HUM. GENETICS 565, 568 (2020).

[102] HARRY KENNEGIESSER, CONCEPTION IN THE TEST TUBE THE IVF STORY: HOW AUSTRALIA LEADS THE WORLD 771–72 (Macmillan 1988).

of IVF in Australia was born in 1980.[103] After much public discussion and Parliamentary action, Maeve's law is now in effect in Australia.[104]

After the law passed both houses of the Australian Parliament on March 31, 2022, the Australian National Health and Medical Research Council posted an announcement on April 10, 2022 for the 2022 Pilot Mitochondrial Donation Pilot Program Grant Opportunity, which aims to "support one Australian medical research and medical innovation project that conducts a pilot program, including a clinical trial, for the purposes of building the evidence base to determine the safety, efficacy and feasibility of implementing mitochondrial donation reproductive technology in clinical practice settings."[105]

Australia is a federal constitutional state.[106] It is composed of nine jurisdictions including the Commonwealth of Australia, six states, and two territories.[107] While Australia has a federal structure in which ART regulation comes from both federal and state sources, only four of the eight Australian states and territories have their own ART

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[103] Ludlow, *supra* note 46, at 5-6 (2020) (citing John Leeton, *The Early History of IVF in Australia and its Contribution to the World*, AUSTL. & N.Z. J. OBSTETRICS & GYNAECOLOGY 495, 496 (2004)).

[104] *See* AUSTL. GOV'T, DEP'T HEALTH, *Legalising Mitochondrial Donation in Australia, Public Consultation Paper*, https://consultations.health.gov.au/strategic-policy/mitochondrial-donation-in-australia/supporting_documents/Mitochondrial%20Donation%20%20Public%20Consultation%20Paper.pdf (requesting public comments by Mar. 15, 2021 and noting that "[t]he Australian Government is proposing to introduce mitochondrial donation in a staged and closely monitored way."); *Mitochondrial Donation*, *supra* note 16..

[105] Media Release, Australian Dep't of Health & Aged Care, Australian Research to Support Children With Mitochondrial Disease (Apr. 11, 2022), https://www.health.gov.au/ministers/the-hon-greg-hunt-mp/media/australian-research-to-support-children-with-mitochondrial-disease; Bulletin from Austln. Gov't Nat'l Health & Medical Resource Council, 2022 Mitochondrial Donation Pilot Program Grant Opportunities (Apr. 10, 2022), https://www.bulletpoint.com.au/wp-content/uploads/2022/06/MRFF-EPCDRI-2022-Mitochondrial-Donation-Pilot-Program-Grant-Opportunity-Guidelines.pdf; Aus. Gov't, Archived Grant Opportunity View – GO5600, Apr. 10, 2022, https://www.grants.gov.au/Go/Show?GoUuid=46103a3e-81c5-49c2-89ce-ddd710e4684d.

[106] Carol A. Brook et al., *A Comparative Examination of Police Interrogation of Criminal Suspects in Australia, Canada, England and Wales, New Zealand, and the United States*, 29 WM. & MARY BILL RTS. J. 909, 911 (2021).

[107] *Id.*; AUSTL. GOV'T, *State and Territory Information*, https://www.australia.gov.au/states.

legislation.[108] Other states rely on the NHMRC's *Ethical Guidelines on Assisted Reproductive Technology in Clinical Practice*.[109]

Similar to the United States, ART regulation in Australia has been described as "splintered."[110] In Australia, the national government creates regulatory schemes surrounding issues like embryo research, the creation of embryos (for research and reproduction), and the accreditation of reproductive clinics, while individual states and territories are "responsible for parentage and ART regulation."[111] The Australian Health Ethics Committee also publishes guidelines, which are being reviewed "specifically for mitochondrial donation."[112] Also, similar to the United States, doctors also engage in self-regulation through the participation in and adherence to guidelines promulgated by various societies.[113]

Until this year, mitochondrial transfer was illegal under Australian law.[114] Before Maeve's Law, it would have violated the Prohibition of Human Cloning for Reproduction Act (PHCR) to

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[108] Karinne Ludlow, *The Policy and Regulatory Context of U.S., U.K., and Australian Responses to Mitochondrial Donation Governance*, 58 JURIMETRICS J. 247, 253 n.42 (2018) ("The states with legislation are New South Wales, South Australia, Victoria and Western Australia."). *See* Assisted Reproductive Technology Act 2007 (N.S.W); Assisted Reproductive Treatment Act 1988 (S.Austl.); Assisted Reproductive Treatment Act 2008 (Vict.); Human Reproductive Technology Act 1991 (W. Austl.).

[109] Ludlow, *supra* note 46, at 10–11.

[110] *Id.* at 4.

[111] *Id.* at 11.

[112] *Maeve's Law Provisions*, *supra* note 50, at 21 (citing NHMRC Submission discussing "Ethical guidelines on the use of assisted reproductive technology in clinical practice and research.").

[113] For more on self-regulation of ART in the U.S., *see* Jennifer L. Rosato, *The Children of Art (Assisted Reproductive Technology): Should the Law Protect Them from Harm?*, 2004 UTAH L. REV. 57, 65 (2004) ("The American Society for Reproductive Medicine ('ASRM') is the primary professional organization that oversees the field of reproductive medicine, and the Society of Assisted Reproductive Technology ('SART'), an affiliated organization, specifically covers IVF programs, in addition to other types of ART programs." (citations omitted)). For more on self-regulation of ART in Australia, *see* Ludlow, *supra* note 109, at 253; NAT'L HEALTH & MED. RSCH. COUNCIL, MITOCHONDRIAL DONATION ISSUES PAPER: ETHICAL AND SOCIAL ISSUES FOR COMMUNITY CONSULTATION (2019), https://www.nhmrc.gov.au/sites/default/files/documents/attachments/Mitchondrial-Donation-Issues-Paper.pdf.

[114] The Honorable Greg Hunt MP, Minister for Health and Aged Care, , *Explanatory Memorandum to Accompany Maeve's Bill*, https://parlinfo.aph.gov.au/parlInfo/download/legislation/ems/r6697_ems_34f56965-6288-4da6-9a02-096f5b58d3c1/upload_pdf/JC001678.pdf;fileType=application%2Fpdf.

develop an embryo containing the genetic material of more than 2 individuals.[115] Similarly, it would have violated the PHCR to make any heritable changes to "the genome of a human embryo for reproductive purposes," meaning that the Australian government interpreted "heritability" to include mitochondrial transfer, similar to the FDA's current interpretation of the word.[116] Like in the United States, mitochondrial transfer in Australia faces opposition from many directions, including Catholic religious figures.[117] Others oppose the use of mitochondrial transfer based on "slippery slope" concerns that using mitochondrial donation could later lead to human reproductive cloning.[118]

In 2018, the Australian Senate examined scientific, legal, and ethical issue related to mitochondrial transfer.[119] After this examination, the Senate issued a report and recommended further consultation with multiple stakeholders and regulatory actors before the process was used in Australian clinical practice.[120] In June 2021, a committee of members of Parliament released a report that recommended a public consultation in relation to proposed legislative changes within Australia to permit mitochondrial transfer.[121] The committee charged with writing the Senate's report concluded by noting that "[t]he committee makes no recommendations as this is a conscience matter."[122]

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[115] *Maeve's Law Provisions*, *supra* note 50, at 11; NAT'L HEALTH & MED. RSCH. COUNCIL,*supra* note 113. .

[116] *Maeve's Law Provisions*, *supra* note 50, at 11.

[117] *See, e.g.*, Marilyn Rodrigues, *Bishops Warn of Risks of Mitochondrial Donation Tech*, CATHOLIC WEEKLY (Mar. 21, 2021), https://www.catholicweekly.com.au/bishops-warn-of-risks-of-mitochondrial-donation-tech.

[118] *Maeve's Law Provisions*, *supra* note 50, at 27.

[119] Explanatory Memorandum, Mitochondrial Donation Law Reform (Maeve's Law) Bill 2021 (Cth) 2 (Austl.), https://parlinfo.aph.gov.au/parlInfo/download/legislation/ems/r6697_ems_34f56965-6288-4da6-9a02-096f5b58d3c1/upload_pdf/JC001678.pdf;fileType=application%2Fpdf.

[120] *Id*.

[121] Nogrady, *supra* note 7; Parliament of Australia, *Report: Science of Mitochondrial Donation and Related Matters, List of Recommendations,* https://www.aph.gov.au/Parliamentary_Business/Committees/Senate/Community_Affairs/MitochondrialDonation/Report/b01.

[122] *Maeve's Law Provisions*, *supra* note 50, at 43; *see Chapter 4: Ethics of Mitochondrial Donation*, AUSTL. COMM. CMTY. AFFS.,

Australia's Minister for Health and Aged Care, the Honorable Greg Hunt MP, introduced Maeve's Bill, his proposal to legalize mitochondrial transfer.[123] Under that proposal, the regulatory framework would focus on the issuance of licenses for mitochondrial transfer being administered by the National Health and Medical Research Council (NHMRC).[124] Currently, the NMHRC maintains that some research could be conducted under current licensing; however, no human clinical use of mitochondrial transfer is permissible at this time.[125] Licenses would be available in 5 stages, which is arguably similar to the FDA's multi-stage drug approval process.[126] The stages of the Australian licenses include research and training licenses, which one might expect would not be required in the U.S. depending on the type of research.[127] In Australia, only 2 mitochondrial transfer techniques would be permitted: maternal spindle transfer and pronuclear transfer.[128] On December 1, 2021, the Australian House of Representatives passed Maeve's bill by a vote of 92 to 29.[129] The bill passed in the Australian Senate in March 2022 .[130]

D. "Comparator" Differences

Before addressing the lessons that the United States might learn from Australia and the U.K., I acknowledge that some would dismiss a comparative approach or emphasize the differences amongst the three countries. There are, admittedly, some differences. One

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https://www.aph.gov.au/Parliamentary_Business/Committees/Senate/Community_Affairs/MitochondrialDonation/Report/c04 (last visited Sept. 22, 2021).

123 *See generally* Explanatory Memorandum, *supra* note 119.

124 *Maeve's Law Provisions*, *supra* note 50, at 3.

125 NAT'L HEALTH & MED. RSCH. COUNCIL, *supra* note 113.

126 *Maeve's Law Provisions*, *supra* note 50, at 5 ("a pre-clinical research and training licence; a clinical trial research and training licence; a clinical trial licence; a clinical practice research and training licence (only available under stage 2); and a clinical practice licence (only available under stage 2)") (citing the Explanatory Memorandum to the Bill); *see also Step 3: Clinical Research*, U.S. FOOD & DRUG ADMIN. (Jan. 4, 2018), https://www.fda.gov/patients/drug-development-process/step-3-clinical-research.

127 *See Maeve's Law Provisions*, *supra* note 50, at 22.

128 *Mitochondrial Donation Law Reform (Maeve's Law) Bill 2021*, *supra* note 15, at 35.

129 Martin, *supra* note 15.

130 *Mitochondrial Donation Law Reform (Maeve's Law) Bill 2021*, *supra* note 15.

noteworthy difference involves the amount of religious influence on regulation varies across the countries. Within the U.K., there are state-sponsored churches, yet many observers view the United States as more religious than the United Kingdom or Australia.[131] In its Supplementary Submission related to Maeve's bill, the Mito Foundation stated that the United States was not an "appropriate comparator" when assessing whether mitochondrial transfer should go forward in Australia because "there are a number of religious and other elements at work in the United States that impact access to women's health, including IVF, birth control, and abortion."[132] While this assessment of the comparative differences between the U.S. and Australia is certainly accurate, the differences between the U.K. and Australia on the one hand and the United States on the other hand, do not hinder the Article's overall aims, which are to foster discourse and to ascertain how one might structure a "piecemeal" or "segmented" approach to the legalization of mitochondrial transfer in the U.S.

Australia has legislation and substantive regulations related to ART, whereas the United States is notable for the lack of clearly applicable federal substantive law related to forms of ART involving genetic innovation.[133] Individuals and governmental actors in the U.S., U.K., and Australia have different views on whether mitochondrial transfer is genetic modification and the significance of that genetic modification.[134] For example, the U.K. Department of Health concluded that mitochondrial transfer was not genetic modification

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131 *See generally* U.S. DEP'T STATE, OFF. INT'L RELIGIOUS FREEDOM, 2020 REPORT ON INTERNATIONAL RELIGIOUS FREEDOM: UNITED KINGDOM (2021), https://www.state.gov/wp-content/uploads/2021/05/240282-UNITED-KINGDOM-2020-INTERNATIONAL-RELIGIOUS-FREEDOM-REPORT.pdf; Dalia Fahmy, *Americans Are Far More Religious Than Adults in Other Wealthy Nations*, PEW RSCH. (July 31, 2018), https://www.pewresearch.org/fact-tank/2018/07/31/americans-are-far-more-religious-than-adults-in-other-wealthy-nations/.

132 MITO FOUND., *Mitochondrial Donation Law Reform (Maeve's Law) Bill* 2021 *Submission 16 – Supplementary Submission*, at 6 (Aug. 10, 2021) (Austl.).

133 *Maeve's Law Provisions*, *supra* note 50, at 1 (Maeve's law would modify the following legislation: "the Prohibition of Human Cloning for Reproduction Act 2002 (PHCR Act)[;] the Research Involving Human Embryos Act 2002 (RIHE Act) [;] the Research Involving Human Embryos Regulations 2017 (RIHE Regulations) [;] the Therapeutic Goods (Excluded Goods) Determination 2018 (Excluded Goods Determination), [;] and the Freedom of Information Act 1982 (FOI Act)").

134 *See* discussion *supra,* Part I., Section B.

whereas currently, the FDA's interpretation of the Congressional budget rider prohibiting "heritable genetic modification" includes mitochondrial transfer.[135]

The three countries analyzed in this Article also have varying views on entitlements to donor information and the significance of genetic donors. In the U.K., mitochondria are generally not seen as significant to identity which, at least in bioethics discourse, tends to focus on nuclear DNA.[136] In the U.K., children conceived as a result of mitochondrial donation would not be entitled to information related to their mitochondrial donor.[137] In the U.S., children created using IVF are not entitled to information related to their donor, whereas Maeve's law will permit children born as a result of mitochondrial transfer to "apply for identifying information about their donor when they turn 18."[138] Similar to the treatment of parentage in the U.S., mitochondrial egg donors in Australia would not be legal parents of the children conceived using mitochondrial transfer, an issue that is resolved by state law in the U.S. as opposed to federal law.[139] Australians have taken a markedly different direction on the issue of sex selection than many Americans. For example, the National Academies of Sciences recommended that only male embryos be implanted in order to avoid issues related to the "heritability" of mitochondrial changes, whereas the Australian legislation leaves the issue of sex selection to the parents.[140]

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[135] *See* Ludlow, *supra* note 108, at 256 ("According to the U.K. Dep't of Health Report, genetic modification requires "germline modification of *nuclear* DNA . . . that can be passed on to future generations.") (citing Public consultations: Health Sci. & Bioethics Div., Dep't of Health, Mitochondrial Donation: Draft Regulations to Permit the Use of New Treatment Techniques to Prevent the Transmission of a Serious Mitochondrial Disease from Mother to Child (2014)); U.S. FOOD & DRUG ADMIN., *Advisory on Legal Restrictions on the Use of Mitochondrial Replacement Techniques to Introduce Donor Mitochondria into Reproductive Cells Intended for Transfer into a Human Recipient* (Mar. 16, 2018), https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/advisory-legal-restrictions-use-mitochondrial-replacement-techniques-introduce-donor-mitochondria; Letter from Mary A. Malarkey, *supra* note 77, at 1.

[136] *See* discussion *supra* Part I.

[137] HUM. FERTILISATION & EMBRYOLOGY AUTH., *supra* note 10.

[138] *See Maeve's Law Provisions*, *supra* note 50, at 7; *Mitochondrial Donation*, *supra* note 16.

[139] *See id.*

[140] *See id.*; NAT'L ACAD. SCIS., ENG'G & MED., *SUPRA* NOTE 2810 (noting the acceptability of sex selection for medical reasons).

In Australia, parents who would use mitochondrial transfer would also be subject to counselling requirements, an approach that seems unlikely in the United States, although issues related to follow-up would likely arise.[141] For example, across the world, follow-up studies are often difficult in ART as happy parents no longer want to continue visiting fertility providers and subjecting children to the requirements of follow-up studies such as tissue samples.[142] Whether parents should be able to decide whether to include their children in future follow-up studies is an ethical issues that arises in discussions of mitochondrial transfer.[143] The U.K.'s mitochondrial donation treatments are accompanied by expected follow-up appointments for children conceived using mitochondrial transfer at eighteen months and five years old.[144] Additionally, while much attention is paid to the issue of physical follow-up, others in Australia have testified to the need for a registry that focuses not only on scientific issues but psychosocial implications.[145] As has arisen in debates regarding ART and all forms of ART involving genetic modification or substitution, observers note that the risks of the techniques to the child and subsequent generations are unknown, however that is the case with many FDA-approved products.[146] Follow-up studies have been recommended a part of recent FDA gene therapy approvals.[147] In light

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141 *See Maeve's Law Provisions*, *supra* note 50, at 19.

142 Lyndsey Craven et al., *Scientific and Ethical Issues in Mitochondrial Donation*, 24 THE NEW BIOETHICS J. 57, 67–68 (2018); *See, e.g.*, Transcript, *Center for Biologics Evaluation and Research, Food and Drug Administration, Biological Response Modifiers Advisory Committee Open Session*, Meeting #32, 375 (May 9, 2002, 8:00 AM), https://www.fda.gov/OHRMS/DOCKETS/ac/02/transcripts/3855t1-01.pdf [https://wayback.archive-it.org/7993/20170404082240/https://www.fda.gov/OHRMS/DOCKETS/ac/02/transcripts/3855t1.htm].

143 *See* T. Ishii, *Should Long-Term Follow-up Post-Mitochondrial Replacement be Left up to Physicians, Parents, or Offspring?*, 25 THE NEW BIOETHICS J. 3 (2018) (arguing for parental determinations of whether to include children in mitochondrial transfer long-term follow-up).

144 Lyndsey Craven et al., *supra* note 142, at 67–68.

145 *See, e.g.*, *Public Hearing Transcript*, *supra* note 10, at 27–28.

146 *Maeve's Law Provisions*, *supra* note 50, at 35.

147 *See, e.g.*, U.S. FOOD & DRUG ADMIN., FDA BRIEFING DOCUMENT: ONCOLOGIC DRUGS ADVISORY COMM. MEETING, BLA 125646, TISAGENLECLEUCEL, NOVARTIS PHARM. CORP. (2017), at 25, https://www.fda.gov/media/106081/download ("In 2006, FDA published recommendations for the long-term follow-up monitoring of gene therapy recipients for delayed adverse events

of the concern for future generations (a concern that generally does not limit natural reproduction), it is possible that, like in Australia, where some have suggested writing follow-up studies into the legislation, the U.S. may, if mitochondrial transfer is approved through FDA regulatory pathways, consider including follow-up studies in future approvals.[148]

Even though the U.K. takes a markedly more restrictive approach to access to donor information in the context of ART, lack of donor information thus far has not precluded IVF's legality in the U.S. and is likely an insignificant factor in regulation.[149] In other words, while some object to mitochondrial transfer as "three-parent IVF," those individuals tend to give little emphasis to the identity or information about that "third parent".[150]

The U.S. is known for its "unregulated" or "minimally regulated" approach to assisted reproductive technology, where only one federal statute, the Federal Clinic Success Rate Act, directly addresses assisted reproductive technology.[151] The U.S. has used budget riders and generally unreviewable agency action to regulate mitochondrial

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(FDA Guidance for Industry: Gene Therapy Clinical Trials—Observing Subjects for Delayed Adverse Events, 2006a)."); *Summary Minutes of the Oncologic Drugs Advisory Committee*, U.S. FOOD & DRUG ADMIN. CTR. FOR DRUG EVALUATION & RSCH. (July 12, 2017), at 6 (transcript available at https://fda.report/media/107129/Minutes-for-the-July-12—2017-Meeting-of-the-Oncologic-Drugs-Advisory-Committee-%28ODAC%29.pdf) ("A committee member stated concern over unknown late toxicities, but that long term survival outweighs that potential risk.").

148 *See Maeve's Law Provisions*, *supra* note 50, at 15; *see also* Karinne Ludlow et al., *Mitochondrial Donation Law Reform (Maeve's Law) Bill 2021 Submission 48* ((noting that the phrasing of the monitoring requirements in the legislation "raises the question of whether children born under a clinical practice license . . . are considered patients . . . and that patient monitoring obligations apply, or whether the intention is that once approved for clinical use, MDT will be treated as any other ART IVF procedure.").

149 *Guidance regarding gamete and embryo donation*, AM. SOC'Y REPROD. MED. (Jan. 20, 2021), https://www.asrm.org/globalassets/asrm/asrm-content/news-and-publications/practice-guidelines/for-non-members/recs_for_gamete_and_embryo_donation.pdf; *Donors*, HFEA (Sept. 18, 2022), https://www.hfea.gov.uk/donation/donors/.

150 As online genetic databases continue to increase in use, anonymous donation may be rendered less anonymous over time. *See generally* Seema Mohapatra, *The Myth of "Anonymous" Gamete Donation in the Age of Direct-to-Consumer Genetic Testing*, *in* CONSUMER GENETIC TECH.: ETHICAL & LEGAL CONSIDERATIONS 94–104 (I. Glenn Cohen, Nita Farahany, Henry Greely, & Carmel Shachar eds., 2021).

151 *See* 42 U.S.C. §§ 263a-1; Lewis, *How Subterranean Regulation Hinders Innovation in Assisted Reproductive Technology*, *supra* note 17, at 1241 n. 1 (providing a literature review).

transfer.[152] Those choices have led to a regulatory standstill. Yet, by targeting forms of ART involving genetic modification for the FDA's investigational new drug requirement, the agency has arguably laid the groundwork for a more HFEA-like regime, like in the U.K. where a government agency is responsible for determining matters such as which ART techniques are available and the conditions under which individuals can access those techniques. Ultimately, differing constitutional structures, varied national- and state-level decisions on matters like donor information, and differing allocations of legal issues to federal and state jurisdiction do not preclude a comparative analysis or the use of solutions based on the Australian or U.K. experiences with mitochondrial transfer. The next Part of the Article identifies useful aspects of the U.K. and Australian approaches to the legalization of mitochondrial transfer in order to make structural suggestions for the U.S. going forward.

III. Segmented Innovation for the United States: Applying the Experiences of the U.K. and Australia to the American Regulation of Mitochondrial Transfer

Mitochondrial transfer is now legal in the U.K. and Maeve's Law has paved the way for its potential clinical use in Australia. In a previous article, I analyzed the United Kingdom's process of legalizing mitochondrial transfer in light of the American "democratic deficit" in the federal regulation of assisted reproductive technology.[153] Regardless of the fate of Maeve's Bill, the processes that Australia and the U.K. have used could provide useful insights to be implemented in the United States. In particular, key lessons include educating the public about the underlying science of these techniques, to minimize sensationalism, and multiple forms of public consultation that extend beyond gathering comments from the public like with notice-and-comment rulemaking.

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[152] *See supra* notes 72-78 and accompanying text.

[153] *See* Myrisha S. Lewis, *The American Democratic Deficit in Assisted Reproductive Technology Innovation*, 45 AM. J.L. & MED. 130, 145–48, 164–68 (2019).

A. Public Consultation Beyond Notice and Comment Rulemaking

Public deliberation or engagement is a broad term that encompasses a number of goals including transparency, education, and "bring[ing] an informed democratic process to decisions."[154] Many methods of deliberative democracy exist, including "public communication," "public consultation," "public involvement," "public collaboration" like consensus conferences, and "public empowerment."[155] Public deliberation or engagement would be useful in the United States as it could serve to (1) educate the public, (2) connect groups that usually do not interface with each other, including federal agency employees and the general public, (3) satisfy scientists' and bioethicists' calls for public consultation in the area of reproductive genetic innovation, and (4) broaden the perspectives available to legislators and agency officials.[156]

Public involvement in decision-making comprises a range of actions from passive (such as soliciting public input) to more active (like voting). Public opinion polls are one method of public engagement; however, they tend to be carried out by non-governmental entities, like the Pew Research Center or the now-defunct Genetics and Public Policy Center at Johns Hopkins University instead of administrative agencies.[157] Public communication can

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[154] *See, e.g.*, NAT'L ACAD. SCIS., ENG'G, & MED., REFLECTING SUNLIGHT: RECOMMENDATIONS FOR SOLAR GEOENGINEERING RSCH. & RSCH. GOVERNANCE 154 (2021); Albert C. Lin, *Mismatched Regulation: Genetically Modified Mosquitoes and the Coordinated Framework for Biotechnology*, 51 U.C. DAVIS L. REV. 205, 230–31 (2017); *see also* KRISTEN L. CARMAN ET AL., REPORT FOR AGENCY FOR HEALTHCARE RESEARCH AND QUALITY, PUBLIC DELIBERATION TO ELICIT INPUT ON HEALTH TOPICS: FINDINGS FROM A LITERATURE REVIEW ii at ES-5, 18-20 ("Public deliberation—a method of public consultation in which members of the public come together to engage in informed dialogue about difficult or complex social issues—can be implemented via several different designs and methodologies.").

[155] Dietram A. Scheufele et al., *What We Know About Effective Public Engagement on CRISPR and Beyond*, PNAS (2021), at 4–5, https://www.pnas.org/doi/epdf/10.1073/pnas.2004835117.

[156] *See also* CARMAN ET AL., *supra* note 154, at ES-4 ("Deliberation is governed by the principle of mutual sharing of perspectives and respect for differing points of view") (citations omitted).

[157] *See* Monique Harris, *Americans Divided Over Genetic Manipulation*, THE GAZETTE ONLINE (Dec. 16, 2002), https://pages.jh.edu/gazette/2002/16dec02/16divide.html [https://www.pewtrusts.org/en/projects/archived-projects/genetics-and-public-policy-center]; Susannah Baruch, *Preimplantation Genetic Diagnosis and Parental Preferences: Beyond Deadly Disease*, 8 HOUS. J. HEALTH L. & POL'Y 245, 252 (2008); Cary Funk et al., *U.S. Public Wary*

include agency outreach and the providing of information; it is often a part of public consultation.[158] Public involvement, which can be part of a public consultation, can also include deliberative opinion polls that assess the views of members of the public before and after expert deliberations.[159] Public consultation, like that which has occurred in the United Kingdom and Australia involves soliciting public feedback and considering as part of the regulatory process.[160] Public empowerment, such as the empowerment that occurs in the context of ballot initiatives in the United States, involves direct decision-making by the public, but is unlikely in the case of mitochondrial transfer at the federal level although it could be possible in an individual state in the future.[161]

In countries that have legalized mitochondrial transfer, public consultation has been a part of the societal and legal conversations.[162] Public consultations, which involve far more outreach than the United States' notice and comment processes, agency-led public meetings, and lack of administrative agency discussion altogether, have been used in both the United Kingdom and Australia.[163] Part of the U.K. and Australian experiences with mitochondrial transfer have included public outreach and a societal discourse. In the United Kingdom, the five-strand public consultation that preceded the legalization of mitochondrial transfer involved "…deliberative public workshops, …[a] public representative survey,…[an] open consultation

of Biomedical Technologies to 'Enhance' Human Abilities, PEW RSCH. CTR. (Jul. 26, 2016), https://www.pewresearch.org/science/2016/07/26/u-s-public-wary-of-biomedical-technologies-to-enhance-human-abilities/.

158 Scheufele et al., *supra* note 155, at 4.

159 *Id*.; *supra* Part III.A.

160 Scheufele et al., *supra* note 155, at 4; *supra* Part III.A.

161 Scheufele et al., *supra* note 155, at 5; *See e.g.,* Julian N. Eule, *Judicial Review of Direct Democracy*, 99 YALE L.J. 1503, 1509 (1990) (discussing state ballot initiatives and other methods of direct democracy).

162 *See* discussion *supra* Part II.

163 *See, e.g.*, 5 U.S.C. § 553; Catherine M. Sharkey, *Federalism Accountability: "Agency-Forcing" Measures*, 58 DUKE L. J. 2125, 2163 (2009) ("Notice-and-comment rulemaking is the means by which federal agencies solicit and incorporate the views of all "interested persons" before issuing final rules."); Nicholas Bagley, *The Procedure Fetish*, 118 MICH. L. REV. 345 (2019); *See supra* notes 40-41 and accompanying text (providing and analyzing a 2014 FDA employee statement at an Advisory Committee meeting).

questionnaire,…open consultation meetings…and patient focus groups."[164]

Citizens' juries or citizens' panels are another method of addressing a "democratic deficit" in regulation as they aim to increase public participation in government.[165] At the same time, critics of citizens' juries note that "[w]hile it is agreed that citizens should share in decision-making, there is no feeling that they should be involved in the process of governing more directly."[166] Citizens' juries have been used to obtain public views on a number of matters related to health care in the United Kingdom and Australia.[167] Citizens' juries are also used in other such as Canada, European Union Member States, the United States, and India.[168] Notably, Professor Ainsley Newson and colleagues convened a citizens' jury on mitochondrial transfer in Australia and published the results.[169]

In Australia, various governmental bodies acted to inform the public and solicit their views. In 2018, the Australian Senate Community Affairs Committee published, *Science of mitochondrial*

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[164] SARAH BARBER & PETER BORDER, MITOCHONDRIAL DONATION 13 (2015), https://researchbriefings.files.parliament.uk/documents/SN06833/SN06833.pdf; James Gallagher, *UK Government Backs Three-Parent IVF*, BBC NEWS (June 27, 2013), www.bbc.co.uk/news/health-23079276 [https://perma.cc/5KDD-LP3F]; HUM.FERTILISATION & EMBRYOLOGY AUTH., ANNUAL REPORT & ACCOUNTS, CHAIR AND CHIEF EXECUTIVE'S FOREWORD 4–5 (2012-2013), https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/246699/0323.pdf.

[165] *See, e.g.*, Lewis, *supra* note 153; Bagley, *supra* note 163, at 372 ("Agencies are also said to labor under an acute democratic deficit: they lack the populist pedigree of either the legislature or the president, yet they wield immense government power."); Susan Pickard, *Citizenship and Consumerism in Health Care: A Critique of Citizens' Juries*, 32 SOC. POL'Y & ADMIN. 226, 226 (1998); Rachel Krinks et al., *Do Consumer Voices in Health-Care Citizens' Juries Matter?*, 19 HEALTH EXPECTATIONS 1015, 1016 (2015).

[166] Pickard, *supra* note 165, at 227.

[167] Gerry King et al., *Exploring Public Perspectives on E-Health: Findings from Two Citizen Juries*, 14 HEALTH EXPECTATIONS 351, 351–59 (2010); Jackie Street et al., *The Use of Citizens' Juries in Health Policy Decision-Making: A Systematic Review*, 109 SOC. SCI. & MED. 1, 1–6 (2014).

[168] Street et al., *supra* note 167, at 1-4; Devidas Menon & Tania Stafinski, *Engaging the Public in Priority-Setting for Health Technology Assessment: Findings from a Citizens' Jury*, 11 HEALTH EXPECTATIONS 282, 285 (2008).

[169] Ainsley Newson et al., *Public Attitudes Towards Novel Reproductive Technologies: a Citizens' Jury on Mitochondrial Donation*, 34 HUM. REPROD. 751 (2019).

donation and related matters.[170] In 2019, the Committee released information related to mitochondrial donation and opened a submission portal so that members of the public could submit their views on mitochondrial transfer.[171] In addition to the Citizens' Jury convened by Professor Newson and colleagues in Australia, the NHMRC convened its own citizens' panel which met over two weekends: once in October 2019 and once in November 2019.[172] As part of the citizens' panel, citizens attended presentations by scientific, medical, legal, and ethical experts. [173] The Citizens' Panel published a statement after its convention.[174] The NHMRC also conducted multiple webinars, posted videos, and used roundtables to solicit the views of experts in the field.[175] In 2020, the NHMRC published the report of the Mitochondrial Donation Expert Working Committee.[176] Later that year, the NHMRC released a report that summarized the agency's findings.[177]

In 2021, as part of the public outreach portion of the leadup to Maeve's bill, the Australian government received 60 submissions in a public consultation.[178] Some submissions were less than 2 pages long

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[170] *See generally* CMTY. AFFS. REFERENCES COMM., SCIENCE OF MITOCHONDRIAL DONATION AND RELATED MATTERS (2018), https://www.aph.gov.au/Parliamentary_Business/Committees/Senate/Community_Affairs/MitochondrialDonation/Report.

[171] *Mitochondrial Donation*, NAT'L HEALTH & MED. RSCH. COUNS. (2019), https://www.nhmrc.gov.au/mitochondrial-donation-0.

[172] AUSTRALIAN GOV'T NAT'L HEALTH & MED. RSCH. COUNS., *Mitochondrial Donation Community Consultation: Citizens' Panel Position Statement 3*, https://www.nhmrc.gov.au/sites/default/files/documents/attachments/Citizens%27-panel-position-statement.pdf [hereinafter NAT'L HEALTH & MED. RSCH. COUNS., *Mitochondrial Donation Community Consultation*].

[173] *Id*.

[174] *Id*. at 2-3.

[175] NAT'L HEALTH & MED. RSCH. COUNS., *Mitochondrial Donation Community Consultation*, *supra* note 172.

[176] *Mitochondrial Donation*, *supra* note 171.

[177] NAT'L HEALTH & MED. RSCH. COUNS., REPORT ON NHMRC'S PUBLIC CONSULTATION ON THE SOCIAL AND ETHICAL ISSUES RAISED BY MITOCHONDRIAL DONATION (CONSULTATION REPORT), file:///C:/Users/bebea/Downloads/Consultation-report.pdf.

[178] *Mitochondrial Donation*, *supra* note 16 ("A public consultation process on the proposed approach to introducing mitochondrial donation in Australia, ran from 5 February 2021 until 15 March 2021."); NAT'L HEALTH & MED. RSCH. COUNS., *Mitochondrial Donation Community*

while others were much longer.[179] Submissions by members of the public also included scientific background including benefits and risks or side effects of the techniques, recommendations for or against the techniques, and questions about aspects and implications of the bill.[180] This effort went beyond the U.S. approach to mitochondrial transfer, which has involved no solicitation of public comment and no discussion through public hearings either. Later, the Article will draw on this combination of public input as combined with legislative hearings that include legislative consideration and expert testimony, as part of its recommendations for the United States.

The Australian Senate's Community Affairs Legislation Committee held "Senate Inquiry Hearings" on August 6, 2021, which involved the testimony of scientists including the President of the ISSCR, George Daley, who is also the Dean of Harvard Medical School.[181] Commenters had access to public submissions before the Senate Inquiry Hearings and several incorporated those submissions into their testimony.[182] The ISSCR supports Maeve's bill "because it would establish a rigorous, incremental approach to enable MRT to prevent the transmission of mitochondrial diseases that is consistent with the process described in the ISSCR guidelines….[and] provides a process for evaluating the safety and efficacy of MRT before making it available more broadly in clinical practice."[183] The ISSCR was also

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Consultation, *supra* note 172.

[179] *See, e.g.*, Mitochondrial Donation Law Reform (Maeve's Law) Bill 2021, Submission 6 (Tiffany Boughtwood, Managing Director, Australian Genomics).

[180] *See, e.g.*, Mitochondrial Donation Law Reform (Maeve's Law) Bill 2021, Submission 53 (Dr. Gregory K. Pike, Director, Adelaide Centre for Bioethics and Culture, *Submission to Senate Community Affairs Committee re Mitochondrial Donation Law Reform Bill*, Aug. 2, 2021); Mitochondrial Donation Law Reform (Maeve's Law) Bill 2021, Submission 55 (Professor Julian Savulescu, Murdoch Children's Research Institute, July 16, 2021); Mitochondrial Donation Law Reform (Maeve's Law) Bill 2021, Submission 4 (Rare Voices Australia Submission, July 2021); Mitochondrial Donation Law Reform (Maeve's Law) Bill 2021, Submission 5 (Monash IVF Group, Jul. 14, 2021). For sources opposed to Maeve's Bill, see, for example, Mitochondrial Donation Law Reform (Maeve's Law) Bill 2021, Submission 7 (Professor Megan Best, University of Notre Dame Australia, Jul. 7, 2021).

[181] *See, e.g.*, Agenda, Public Hearing, THE SENATE CMTY. AFFS. LEGIS. COMM, *Mitochondrial Donation Law Reform (Maeve's Law) Bill 2021*, Aug. 6, 2021, https://www.aph.gov.au/Parliamentary_Business/Committees/Senate/Community_Affairs/MitochondrialLawReform/Public_Hearings; *Public Hearing Transcript*, *supra* note 10, at 19–27..

[182] *See, e.g.*, *Public Hearing Transcript*, *supra* note 10, at 9.

[183] Mitochondrial Donation Law Reform (Maeve's Law) Bill 2021, Submission 9 (Melissa H.

cited in the National Academies *Mitochondrial Replacement Techniques* report as having established guidelines for the ethical use of human embryos in research.[184] Thus, in addition to examining the successful experiences of other countries, when considering the future of mitochondrial transfer in the U.S., governmental actors should consider that groups in the U.S. and abroad have already contributed to an expert consultation process.

In the United States, agencies have used some of the techniques of public involvement, but more can be done. The Department of Health and Human Services used public outreach methods such as "listening sessions" in the leadup toward establishing "essential health benefits" even though it was not required by the Administrative Procedure Act.[185] Thus, although the FDA, an operating division of the U.S. Department of Health and Human Services is not known for taking such a public-facing approach on issues of moral, political, or social controversy, it could certainly do so.[186] Increasing public interactions outside of the notice and comment process might have an "equalizing" impact on access, as many FDA employees speak at industry events (often with financial requirements for attendance) or interface with patients through FDA-established patient groups, but these interactions do not include the general public.[187] Beyond that, there are many options for public engagement, as identified by a report issued by another operating division of the U. S. Department of Health and Human Services, the Agency for Healthcare Research and Quality.[188] Even if the FDA did not lead efforts at public engagement and those efforts were left to other sponsors like individual state actors or private

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Little, President, ISSCR, July 16, 2021), *available at* https://www.isscr.org/isscr-news/the-isscr-comments-on-the-australian-mitochondrial-donation-bill.

184 NAT'L ACAD. SCIS., ENG'G & MED., *supra* note 28, at 12.

185 Nicholas Bagley & Helen Levy, *Essential Health Benefits and the Affordable Care Act: Law and Process*, 39 J. HEALTH POL. POL'Y & L. 441, 443–49 (2014).

186 *See About HHS*, U.S. DEP'T HEALTH & HUM. SERVS., https://www.hhs.gov/about/agencies/hhs-agencies-and-offices/index.html.

187 *See, e.g.*, Molecular Med. Tri-Conference, Interview of Peter Marks by Christine Lingham, Mar. 1-4, 2020, https://www.triconference.com/transcripts/peter-marks-transcript; Food and Drug Law Institute, *Fundamentals of Vaccine Regulation: Scientific Ingenuity and Rigorous Review, Feb. 4, 2021 Virtual Course*, https://www.fdli.org/2021/02/fundamentals-of-vaccine-regulation-scientific-ingenuity-and-rigorous-review/.

188 CARMAN ET AL., *supra* note 154; *About HHS*, *supra* note 186.

groups, there would still be some value to obtaining societal perspectives and fostering societal discourse on techniques involving reproductive genetic innovation. As legislators and interested parties continue to consider the legal framework that will accompany techniques involving genetic changes in the United States, it is worth framing those techniques in a manner that is accessible to the public and that minimizes the sensational views that accompany reproductive genetic innovation.

Constructing a public consultation related to mitochondrial transfer would exceed the space allotted in this Article, but this Article notes some of the areas that could be considered in that consultation.[189] Such a consultation could be conducted at the federal level, by the U.S. Food and Drug Administration (because it is currently seen as the regulator of these techniques) or by other agencies within the U.S. Department of Health and Human Services, such as the National Institutes of Health, which is arguably more interested in the educational and bioethical aspects of medical innovations.[190]

Part of that consideration should likely include the stories of individuals who have used the techniques. While many who are seeking to have pharmaceuticals approved by the FDA have been vocal (and successful) at having those pharmaceuticals approved, those interested in using reproductive genetic innovation have been less successful and visible. Part of an American public consultation, whether orchestrated by Congress, the FDA, or another administrative agency, should include stories from individuals who have suffered

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[189] In a companion article, I have emphasized the potential usefulness of a discourse related to all techniques involving reproductive genetic innovation, which includes cytoplasmic transfer, mitochondrial transfer, and germline gene editing. *See* Myrisha S. Lewis, *Normalizing Reproductive Genetic Innovation* (on file with author).

[190] In the past, the NIH administered a Consensus Development Review program which fostered communications among experts on various medical topics. *See* THOMAS STARZL, PUZZLE PEOPLE: MEMOIRS OF A TRANSPLANT SURGEON 162, 252-54, 269 (U. of Pitt. Press 1992); *NIH Consensus Development Program, Retirement of the National Institutes of Health Consensus Development Program*, NAT'L INSTS. HEALTH, https://consensus.nih.gov. The NIH is not necessarily neutral as it has expressed an opposition to applications involving germline genetic modification for decades. *See* Carrie D. Wolinetz & Francis S. Collins, *NIH Supports Call for Moratorium on Clinical Uses of Germline Gene Editing*, 567 NATURE 175 (2019), https://www.nature.com/articles/d41586-019-00814-6. In terms of bioethical conversations, the NIH has a Department of Bioethics which currently offers consultation services in connection with patient care and clinical research at the NIH. *See Bioethics Consult Service*, NAT'L INSTS. HEALTH, https://www.bioethics.nih.gov/clinical/index.shtml.

from mitochondrial disease and who might also want to avail themselves of these technologies.[191] Furthermore, it might be useful to have the perspectives of those who have used or been conceived using cytoplasmic transfer as that is the most similar technique of reproductive genetic innovation that has been used in the U.S.[192] Similarly, stakeholder perspectives, including those of individuals who have obtained mitochondrial transfer or who wish to do so, would likely need to be represented. For example, "the lobbying for universal [newborn] screening [in the U.S.] relied on dramatic testimonies of parents."[193] Patient perspectives have been included within FDA Advisory Committees for years. For example, in response to Executive direction, the FDA added voting patient representatives to FDA Advisory Committees tasked with addressing cancer-related issues.[194] While there is a debate within the FDA literature on the appropriateness of patient perspectives in regulatory decisions (and the connection between those patient perspectives and drug approval), the FDA's Patient Representative Program appoints individual patients and advocates as "Special Government Employees," if they are not already "regular" government employees who are then able to provide "direct input to agency staff … on their experiences with various diseases, conditions, and devices while gaining access to

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[191] *See, e.g.*, Mitochondrial Donation Law Reform (Maeve's Law) Bill 2021, Submission 16 (Mito Foundation, Jul. 16, 2021, Appendix One-Case Study: Shelley's Story) (providing the story of Shelley Beverley).

[192] *See* discussion *supra* Part I (discussing cytoplasmic transfer, a technique that is like mitochondrial transfer).

[193] STEFAN TIMMERMANS & MARA BUCHBINDER, SAVING BABIES?: THE CONSEQUENCES OF NEWBORN GENETIC SCREENING 45-48, 59 (University of Chicago Press, 2012) (discussing the "contrast between advocacy narratives and the scientific reports").

[194] *See* White House, Office of the Press Secretary, *Briefing by the Vice President and Dr. David Kessler,* FED. DRUG ADMIN. (Mar. 29, 1996), https://clintonwhitehouse6.archives.gov/1996/03/1996-03-29-briefing-by-vice-president-and-dr-kessler.html ("Third, we will include representatives of cancer patients in FDA's cancer advisory committees and thereby make sure that their views are heard when it comes to recommending approval or nonapproval of cancer drugs."); *Evolution of patient engagement at FDA*, U.S. FOOD & DRUG ADMIN. (Nov. 15, 2019), https://www.fda.gov/about-fda/office-clinical-policy-and-programs/evolution-patient-engagement-fda-text-alternative;
Reinventing the Regulation of Cancer Drugs, U.S. FOOD & DRUG ADMIN. (March 1996), https://web.archive.org/web/20040417225410/http://www.fda.gov/cber/genadmin/reincanc.htm.

confidential information."[195] FDA Patient Representatives also interface with other groups of experts who are affiliated with the FDA such as members of Advisory Committees.[196] Currently, the FDA Patient Representative program encompasses a number of "recruitment areas" including naloxone use, obesity, HIV, and retinitis pigmentosa.[197] This program, however, is not sufficient as a public consultation because it does not resolve transparency concerns but rather leads to a different kind of influence on agency decision-making that is still outside of public scrutiny.[198]

There are disadvantages to public consultations. For example, the lack of a public consultation can permit an issue to remain unregulated and thus legal, like surrogacy in some states, or in vitro fertilization in general, which is viewed as unregulated.[199] Yet, while there has been no public consultation related to mitochondrial transfer, the lack of a public consultation has also corresponded with concise but highly effective federal regulation. In the U.S., a future public consultation could include several issues including explanations of the science of mitochondrial transfer, the role of the FDA in product approval, the limitations of FDA approval, the impacts of state and federal actions on parental and reproductive autonomy, disability rights, and other ethical issues that accompany the use of mitochondrial transfer.[200]

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[195] *About the FDA Patient Representative Program*, U.S. FOOD & DRUG ADMIN. (May 3, 2018), https://www.fda.gov/patients/learn-about-fda-patient-engagement/about-fda-patient-representative-program; *see also* Kyle T. Edwards, *The Role of Patient Participation in Drug Approvals: Lessons from the Accelerated Approval of Eteplirsen*, 72 FOOD & DRUG L.J. 406, 415–16 (2017); Kyle T. Edwards, *Good and Bad Patient Involvement: Implementing the Patient-Involvement Provisions of the 21st Century Cures Act at the FDA*, 128 YALE L. J. F. 1077, 1081 (2019).

[196] *About the FDA Patient Representative Program*, *supra* note 195.

[197] *Id*.

[198] *See* Edwards, *supra* note 195, at 440 (noting that patient pressures are generally regarded as separate from political pressure or influence).

[199] *See, e.g.*, Chris Steller, *Surrogacy Policies Need More Thoughtful Development, Committee Votes*, MINN. STATE LEG. (Mar. 5, 2015, 5:32 PM), https://www.house.leg.state.mn.us/sessiondaily/SDView.aspx?StoryID=5558; Rebecca Beitsch, *STATELINE-As Surrogacy Surges, New Parents Seek Legal Protections*, REUTERS (June 29, 2017, 10:59 AM), https://www.reuters.com/article/stateline/stateline-as-surrogacy-surges-new-parents-seek-legal-protections-idUSL1N1JQ0YD; Michele Goodwin, *Prosecuting the Womb*, 76 GEO. WASH. L. REV. 1657, 1693 (2008).

[200] *See, e.g.*, discussion *supra* Part I.B.

B. Re-interpretation or Removal of the Recurring Federal Budget Rider

As noted in Part II, in 2015, a rider limiting FDA consideration of applications involving "heritable genetic modification" was added to the 2016 budget.[201] This budget rider has been renewed each fiscal year since it was approved in 2015.[202] In general, federal budget riders typically occur without much substantive discussion.[203] There are drawbacks to any approach that involves the federal government: namely, that any such approach would strengthen a current trend of increasing federal regulation of the legality of assisted reproductive technology.[204]

Although budget riders typically occur without much substantive discussion, the U.S. could have a much larger conversation surrounding the currently recurring budget rider.[205] Part of that conversation could include the testimony of individuals who are affected by mitochondrial disease, as there has been a lack of that perspective in the limited conversations held in the U.S. This conversation could motivate the FDA to change its currently overbroad interpretation of heritable genetic modification as including

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[201] Consolidated Appropriations Act of 2016, Pub. L. No. 114-113, § 749, 129 Stat. 2283, 2283 (2015).

[202] *Id*. (prohibiting the FDA from consider applications involving "heritable genetic modification."). While the budget rider focuses on a clinical investigation and the domestic creation of a "genetically modified embryo," neither the budget rider nor the FDA's letter to Dr. John Zhang addresses the potential role of foreign clinical trials in support of a BLA or IND application. Letter from Mary A. Malarkey, *supra* note 77, at 1; *Guidance for Industry and FDA Staff: FDA Acceptance of Foreign Clinical Studies Not Conducted Under an IND: Frequently Asked Questions*, U.S. FOOD & DRUG ADMIN. (March 2012), https://www.fda.gov/media/83209/download; O'Connell et al., *supra* note 77; 21 C.F.R. § 314.106 (2022).

[203] Richard J. Lazarus, *Congressional Descent: The Demise of Deliberative Democracy in Environmental Law*, 94 GEO. L.J. 619, 660 (2006); Sandra Beth Zellmer, *Sacrificing Legislative Integrity at the Altar of Appropriations Riders: A Constitutional Crisis*, 21 HARV. ENV'T. L. REV. 457, 500, 510 (1997); I. Glenn Cohen et al., *Gene Editing Sperm and Eggs (not Embryos): Does it Make a Legal or Ethical Difference?*, 48 J. LAW, MED. & ETHICS 619, 620 (2020).

[204] *See e.g.* Myrisha S. Lewis, *Halted Innovation: The Expansion of Federal Jurisdiction over Medicine and the Human Body*, 2018 UTAH L. REV. 1073 (2018).

[205] Spivak et al. , *supra* note 76; *Consolidated Appropriations Act of 2016*, Pub. L. No. 114-113, § 749, 129 Stat. 2283, 2283 (2015) (prohibiting the FDA from consider applications involving heritable genetic modification).

mitochondrial transfer, or influence Congress to write a narrower budget rider (or none at all).[206] At the same time, the budget rider could have been intended to not only preclude use of the technique in the United States, but also to discourage discussion of the technique at the administrative agency level all together.

C. Substantive Congressional Hearings

Moreover, while there have been conversations and testimony at the level of Congressional subcommittees, perhaps the U.S. should also consider substantive legislation on mitochondrial transfer. At the very least, Congress should convene hearings related to the technique in order to foster conversation similar to what occurred with organ transplantation decades ago, especially if political and social views will impact regulatory decision-making.[207]

Congressional hearings could be useful not only as they related to the recurring budget rider but also in terms of a broader societal discourse. Mitochondrial replacement therapy does not appear to be a priority on any state or federal legislative agenda. Similarly, there seems not to be a "Maeve" in the United States who has influenced the writing of proposed legislation, but there could be. Personal stories and emotional pleas have also resulted in (and accompanied) legislative and policy changes in various health areas including newborn screening and research, treatment, funding, and advocacy for HIV/AIDS, abortion, and breast cancer.[208] Moreover, public consultation could be employed in the U.S. in at least two ways. First, any reporting related to public workshops could be shared with

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[206] Lewis, *How Analogizing Socio-Legal Responses to Organ Transplantation Can Further the Legalization of Reproductive Genetic Innovation*, *supra* note 17, at 671.

[207] These proposed hearings would be more substantial than the hearing that a House subcommittee hearing held in 2015 related to human gene editing. *See The Science and Ethics of Genetically Engineered Human DNA Before the Subcomm. on Research & Tech. of the H. Comm. on Sci., Space, & Tech.*, 114th Cong. 23 (2015), https://www.govinfo.gov/content/pkg/CHRG-114hhrg97564/pdf/CHRG-114hhrg97564.pdf. Not all scholars believe societal views should be significant to debates over the legalization of forms of ART. For example, Prof. Alison Murdoch notes that "society is not harmed by these techniques, neither are any other people within society," when emphasizing that parents have to raise children with serious disability. *See* Alison Murdoch, *IVF and the Prevention of Mitochondrial DNA Disease: The Moral Issues*, BIONEWS (May 3, 2011), https://www.bionews.org.uk/page_92949; *see also* Jussi Niemelä, *What Puts the "Yuck" in the Yuck Factor?*, 25 BIOETHICS 267, 279 (2011).

[208] TIMMERMANS & BUCHBINDER, *supra* note 193, at 226.

legislators, similar to how evidence from the United Kingdom's public workshops was synthesized in a report that was made available before Parliament changed the U.K. law on mitochondrial transfer.[209] Second, educating legislators about mitochondrial transfer, similar to the education that individual U.K. participants in HFEA-sponsored deliberative workshops, could change regulatory perspectives, including the views of those who may be indifferent to mitochondrial transfers use in the United States.[210]

A broader lesson from the Australian approach to the legalization of mitochondrial transfer is one in which the United States' inquiry into the legalization of mitochondrial transfer occurs in an incremental manner. Australia pursued a "staged" approach to the potential legalization of mitochondrial transfer.[211] A "cautious, staged" approach was mentioned by the National Academies of Sciences when they explained the type of trial design that would need to take place in clinical investigations related to mitochondrial transfer.[212]

One issue that arises in the context of public consultations is what the impact of negative perspectives is on regulatory outcomes. One might ask: does opposition automatically veto mitochondrial transfer or similar reproductive genetic innovation techniques? In Australia, even though many opposed mitochondrial donation, the government continued to go forward.[213] Similarly, in the U.K., negative views did not prohibit the legalization of mitochondrial transfer. One can expect that there will be negative views related to the legalization of mitochondrial transfer in the U.S., yet those negative views should not necessarily serve as a veto on the legalization of the technique. One can expect that any discourse in the U.S. would likely result in significant opposition from various groups including religious groups and those who are opposed to genetic innovation more broadly. Yet, such groups are opposed to several other techniques that continue to go forward in

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209 *See e.g.* ADVICE TO GOVERNMENT, *supra* note 47, at 3-4.

210 *Id*. at 29-31 (noting instances in which some stakeholders and participants changed their perspectives on issues such as the amount of regulation of mitochondrial transfer, the appropriate role of the regulator, and access to donor information after participating in the UK's public consultation surrounding mitochondrial transfer).

211 NAT'L HEALTH & MED. RSCH. COUNCIL, *supra* note 113.

212 NAT'L ACAD. SCIS., ENG'G & MED., *supra* note 28, at 12.

213 *Maeve's Law Provisions*, *supra* note 50, at 11.

the U.S., such as stem cell research, abortion, in vitro fertilization and cryopreservation of eggs and embryos. While religious views have certainly precluded funding and led to substantial restrictions in access to techniques (including, especially abortion), thus far, they have not managed to completely ban the underlying techniques in the way that reproductive genetic innovation has been stymied in the U.S. Further, an emphasis on education may serve a particularly limited role in the United States, as illustrated by recent political opposition and public resistance to public health measures intended to reduce the spread of the COVID-19 pandemic although the U.K. has also experienced that resistance.[214] Yet, if education fails to sway participants toward legalizing mitochondrial transfer, that education would still be useful in increasing knowledge and also would result in the maintenance of the *status quo* related to the legality of mitochondrial transfer in the U.S. Moreover, to the extent that religious, ethical, or moral views are prohibiting the use of reproductive genetic innovation in the U.S., public consultations and Congressional hearings can identify those views and facilitate a conversation as to exactly how influential these views should be.

CONCLUSION

A "staged" or incremental approach still does not eliminate or resolve many of the ethical debates and arguments that accompany ART and forms of ART involving genetic modification or substitution like embryo destruction, long-term effects, sex selection, and entitlement to donor information.[215] It does, however, provide a structure for discussing those issues in a more transparent and publicly available manner than they are currently addressed in the U.S. It is possible that the United States needs more time with mitochondrial transfer than the United Kingdom and Australia before

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[214] Lu He *et al., Why do people oppose mask wearing? A comprehensive analysis of U.S. tweets during the COVID-19 pandemic*, 28 J. AM. MED. INFORMATICS ASSOC. 1564, 1570-71 (2021); Holly Ellyatt, *Mask-wearing becomes a new battleground in England as Covid rules are eased* (Jul. 6, 2021 at 5:30 A.M. EDT), CNBC, https://www.cnbc.com/2021/07/06/wearamask-mask-wearing-becomes-a-new-battleground-in-england.html.

[215] *See, e.g.*, Submission 24 (Australian Christian Lobby (ACL) Submission to the Inquiry into the Mitochondrial Donation Law Reform (Maeve's Law) Bill 2021), at 15.

approving it. As that time unfolds, there are many scientific, ethical, and safety issues to discuss and several blueprints available on how to conduct those discussions.