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Perspective

Disruptive Synergy: Melding of Human Genetics and Clinical Assisted Reproduction

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SUMMARY

The melding of human genetics with clinical assisted reproduction, now all but self-evident, gave flight to diagnostic and therapeutic approaches previously deemed infeasible. Preimplantation genetic diagnosis, mitochondrial replacement techniques, and remedial germline editing are particularly noteworthy. Here we explore the relevant disruption brought forth by coalescence of these mutually enabling disciplines with the regulatory and legal implications thereof.

The history of science is rife with examples of disruptive synergy made possible by mutually enabling disciplines. Recombinant DNA technology came to be by applying newly discovered restriction endonucleases to the field of bacterial genetics.[1] The Human Genome Project materialized by pairing high-throughput sequencing with high-performance computing.[2] Induced pluripotent stem cells were realized by bringing transcription factors to bear on the field of nuclear reprogramming.[3] Equally impressive returns have followed the melding of human genetics with clinical assisted reproduction. Striking advances in diagnosis and therapy inevitably followed. In this review, we explore the disruption brought forth by the coalescence of human genetics and clinical assisted reproduction with the regulatory and legal implications thereof.

Preimplantation Genetic Diagnosis (PGD)

Not until the advent of PGD, also known as preimplantation genetic testing for monogenic/single gene disorders (PGT-M), did the synergy inherent in joining human genetics and clinical assisted reproduction become so patently apparent.[4] Designed to screen preimplantation embryos for established gene mutations, PGD grew into the first truly prenatal genetic screening test. PGD transformed prenatal screening from being focused on gestational detection to being intent on preimplantation ascertainment. A method to preclude transmission of heritable maladies by couples at risk was finally at hand. Now practiced the world over, PGD helps to reduce the global burden of genetic disease.

PGD enables couples at risk for heritable monogenic disorders to identify unaffected embryos for uterine transfer.[5] However, PGD delimits the number of transfer-eligible embryos. Concurrent advanced maternal age may further curtail the complement of transferrable embryos.[6] It follows that PGD cycles are routinely associated with a limited complement of transferable embryos. Lower birth rates are bound to follow. A recent series of 2,000 PGD cycles whose birth rate (18%) was markedly reduced compared with non-PGD counterparts (38%) drove home this reality.[7] Considerably worse live birth rates (2.6%) were noted for a total of 38 PGD cycles in search of "savior siblings" for treatment of Fanconi anemia.[8] Given the aforementioned odds, couples at risk for heritable disorders should prepare for multiple PGD cycles in the hope of securing a successful outcome. Inevitable as this state of affairs may be, it is far from optimal. The attendant high costs, inevitable discomfort, and mental anguish are grim reminders of PGD's limitations. Viewed in this light, the case for safe and efficacious future remedial germline editing is compelling. Recent calls to ban remedial germline editing on the grounds that an alternative (i.e., PGD) exists fail to take into account the significant shortfalls of PGD.[9]

Far less clarity marks the validity of a related analytic: PGT for aneuploidy (PGT-A).[10,11] Designed to assess the ploidy status of blastocyst-stage embryos by way of a trophectoderm biopsy, PGT-A aims to reduce early fetal loss by selecting euploid embryos. Although plausible in principle, the blastocyst's innate karyotypic heterogeneity undermines PGT-A's predictive utility.[11,12] Additional doubts regarding the utility of PGT-A were raised by the observation of euploid newborns whose blastocysts of origin were deemed to be aneuploid.[11] Moreover, a carefully designed and executed recent randomized trial concluded that "PGT-A did not improve overall pregnancy outcomes."[13] Professional practice committees have articulated these and related concerns, decreeing that "the value of PGT-A as a screening test…has yet to be determined."[14]

Mitochondrial Replacement Techniques (MRTs)

The prevention of heritable disorders of mitochondrial origin emerged as yet another example of the synergy attained by pairing human genetics with clinical assisted reproduction.[15,16] Arising by way of matrilineal transmission, mitochondrial DNA diseases are highly disabling afflictions.[17,18] As many as 944

and 152 affected children are estimated to be born annually in the United States and United Kingdom, respectively.[19] Many succumb at an early age. Meaningful palliation, much less a cure, remain distant goals.[17,18] MRTs involve replacing the mutation-bearing mitochondria of zygotes or oocytes with wild-type donor counterparts. This allows prospective parents to produce children without mitochondrial DNA diseases who nevertheless remain genetically related to them.

First conceptualized in 1995, MRTs have been the subject of much discussion, focused on two particular techniques.[20,21] Pronuclear transfer (PNT) involves isolation and transfer of the male and female pronuclei of at-risk human zygotes to an enucleated disease-free donor zygote, which, in turn, gives rise to potentially transferable embryos.[22,23] PNT may enable development of blastocyst-stage embryos without increasing the incidence of aneuploidy or gene expression patterns and with a carryover of mutant maternal mitochondrial DNA (mtDNA) that is less than 2% in most PNT-derived blastocysts.[22,23] Maternal spindle transfer (MST) involves isolation and transfer of the metaphase II spindle complex of an at-risk oocyte to an enucleated disease-free donor egg to reconstitute and fertilize oocytes to produce potentially transferrable embryos.[24,25] It is thus an embryo-sparing option. Studies of MST with human oocytes were associated with normal fertilization rates, virtual donor homoplasmy, and metabolic rescue in derived embryonic stem cell lines.[26,27]

Government-sanctioned first-in-human clinical trials of MRT are presently underway in the United Kingdom.[21] It is up to these United Kingdom-based trials to establish MRT as safe and effective. No such clinical trials are anticipated in the United States, where a statutory moratorium on "heritable genetic modification" remains in force.[28]

Comparing the legal regulation of MRT in the two countries is instructive. The United Kingdom approach results from a multi-year process that engaged the public and lawmakers and ultimately led to official regulations in 2015. Enabling legislation empowers the Human Fertilization and Embryology Authority (HFEA) to grant a license to a specific fertility clinic after it has confirmed that the facility can perform PNT and/or MST (other techniques, such as polar body transfer, are not currently permitted). The 2015 regulations permit MRTs only when there is a particular risk that an egg (or embryo created with such egg) may have mitochondrial abnormalities caused by mtDNA and that a person possessing such abnormalities will have or develop a serious mtDNA disease. Use for mere infertility is thus prohibited. Finally, the fact that a particular clinic is licensed to perform PNT and/or MST does not give it carte blanche to offer that procedure to a female patient determined to have heritable mitochondrial abnormalities caused by mtDNA. Instead, any woman seeking MRT would require approval of her case by the HFEA's Statutory Approvals Committee. As of the time of this writing, no live birth following an MRT has been reported in the United Kingdom.[28]

In the United States, in contrast, performing MRTs would violate federal law. The National Academy of Medicine (then called the Institute of Medicine) recommended that the US Food and Drug Administration (FDA) permit initial clinical investigations to go forward (i.e., like other therapeutics, the FDA would conduct its typical premarket review process), subject to several preconditions. These included establishing the safety and risk minimization of MRTs, including *in vitro*, animal and other testing; limiting clinical investigation to women with serious mtDNA diseases whose offspring was at risk of severe medical consequences; using non-viable human embryos to develop the science where possible and, where not possible, minimizing the number of viable embryos and using those that were least developed; and initially limiting intrauterine transfer to male embryos (to avoid transmission of alterations to mtDNA) and moving to female embryo transfer only after several additional requirements were met.[29]

Unfortunately, these recommendations went unheeded; while the report was being developed, Congress passed the aforementioned Consolidated Appropriation Act of 2016, which directs the FDA to refrain from considering applications for "an exemption for investigational use. .in research in which a human embryo is intentionally created or modified to include a heritable genetic modification."[30] The rider was reintroduced and passed by every successive Congress, although in 2019, there was an unsuccessful attempt to alter the legislation during the appropriations process and some discussion of exempting MRTs from the prohibition.[28] Although MRTs remain unlawful to perform in the United States, some have tried to skirt the prohibition by moving some parts of the MRT process offshore. Possibly for the first time, MRTs may have prevented heritable transmission of a fatal mtDNA disease (Leigh syndrome).[20] The procedure, carried out by a United States-led team, took place in Mexico, in conflict with extant FDA policy.[31] Forced to act, the FDA asserted its jurisdiction in this matter and issued a warning letter to those involved.[31]

Beyond the United States and United Kingdom, Australia, Canada, Germany, Israel, and Singapore have developed their own policies regarding MRTs, with some taking more and some less permissive approaches.[28]

Some of the most interesting questions scholars have raised include the following. When might there be civil liability in some legal systems for poor outcomes as part of MRTs?[32–38] For jurisdictions that prohibit gamete donor anonymity and allow donor-conceived children identifying information about their sperm or egg donor, should that rule apply to the mitochondrial donor in MRTs? Do mitochondrial donors have any legal parenthood rights or obligations to the offspring of MRTs? Can mitochondrial donors be paid for their gametes? Should state-financed health care systems cover MRTs on par with other reproductive technologies? How should human rights law relevant to gene editing apply or not apply to MRTs?[28]

Remedial Germline Editing

The latest embodiment of the synergy between human genetics and clinical assisted reproduction revolves around the prospect of remedial germline editing.[39] Absent clinical assisted reproduction, even the concept of remedial germline editing would not exist.[40] Although years away from the clinic, remedial germline editing promises to prevent inborn maladies beyond the reach of current medical therapy.[39] Early pre-clinical studies have so far been limited to the proof-of-concept variety.[41] The most exhaustive such study set out to substitute the mutant

(ΔGAGT) autosomal allele of the *MYPBC3* (hypertrophic cardiomyopathy) gene with its wild-type analog.[42] Editing at the time of fertilization gave rise to an overall targeting efficiency of 72%.[42] Note was also made of insertions, deletions, and mosaicism, which highlight the formidable technical impediments that must be negotiated for remedial germline editing to become a reality.[39,42] Until such time, the transfer of an edited embryo is tantamount to medical malpractice not unlike that recently perpetrated by an apparent rogue actor in China.[43] A statuary prohibition against remedial germline editing is an additional roadblock to its advent in the United States.[34] Absent congressional course correction, no relevant clinical trials are to be anticipated in the United States in the near term.

The subject of international summits, international commissions, committee reports, and position statements, therapeutic germline modification remains a heated topic. The National Academy of Medicine and the Nuffield Council on Bioethics have acknowledged that principled remedial germline editing is worth pursuing in the absence of iatrogenic harm. The National Academy of Medicine recommended that clinical trials of remedial germline editing be limited to "preventing a serious disease or condition" in the "absence of reasonable alternatives."[44] The Nuffield Council on Bioethics went a step further by granting conditional support to remedial germline editing.[39] Both bodies argue in favor of limiting rather than prohibiting current pre-clinical research or future clinical trials of remedial germline editing. Additional guidance regarding the conduct of remedial germline editing is likely forthcoming from reports of the International Commission on the Clinical Use of Human Germline Genome Editing and of the World Health Organization (WHO) Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing.[45,46]

Most objections to remedial germline editing pertain to its premature actualization in China by way of assisted reproduction.[43] The wrong lesson to learn is that we should regulate or prohibit relevant pre-clinical research where none of the edited embryos are slated for uterine transfer.[47,48] Quite the contrary. Understanding the risks associated with remedial germline editing demands that relevant pre-clinical research proceed unfettered. Responsible surveillance of pre-clinical research is readily accomplishable via institutional biosafety committees and embryo research oversight committees, in keeping with guidelines issued by the International Society for Stem Cell Research.

As a practical matter, no national prohibition will preclude its citizenry from accessing advanced reproductive technologies. Medical tourism will see to that. Faced with a legal ban on "heritable genetic modification," United States citizens are likely to seek out more permissive jurisdictions.[31] There must be international coordination if we are to assure responsible oversight of leading-edge assisted reproductive technologies. Precedents abound. International treaties pertaining to chemical weapons, landmines, and intercountry adoption have been successfully negotiated. An international treaty directed at byproducts from melding of human genetics and clinical assisted reproduction deserves serious consideration.

It is the view of many that genes comprise humanity's common heritage, dignity, and diversity. Heritable editing of the human genome, therefore, has the potential to alter the human essence. Additionally, ethical and faith-based concerns exist. It follows that the scientific cognoscenti alone must not decide the disposition of remedial germline editing. Instead, heavy reliance must be placed on participatory public engagement. Such an approach will not only debunk unhelpful fictions—namely, that "designer babies" are just around the corner—but will also improve comprehension of key distinctions, such as between somatic and germline gene editing. Hardly an easy feat, engaging the public is nevertheless wholly doable. A fine example of such an undertaking preceded the parliamentary debate on legalization of MRT in the United Kingdom.[17] Exercising this form of deliberative democracy is required if we are to reach an international consensus regarding the application of remedial germline editing.

The Indispensability of Public Participation

Contending with scientific paternalism, a powerful historic trend, remains a challenge. Influential American philosophers such as John Dewey criticized scientific paternalism, asserting that "lay deliberation and technical expertise can enrich each other.[49] It was only more recently that the notion of public participation in the articulation of science policy came to the fore. Several strong arguments support engaging the public's input. First, a dubious unengaged public may be hard pressed to accept scientific input. Second, the public's input is well worth hearing. The value added is a perspective the scientific community might not have realized. Third, the buy-in of the public on all matters science must be a given in a democratic society. Failing to embrace these principles portends failure. It is in this context that the Center for Public Engagement with Science & Technology of the American Association for the Advancement of Science could take the lead in assuring the public's participation.[50]

Conclusions

The recent past has witnessed some of the most disruptive developments in the co-evolution of human genetics and clinical assisted reproduction. Facing up to the attendant challenges requires learning from the past. Hopeful hype, fabricated fears, or casting regulatory questions in Manichean terms will not point the way. What is needed is a subtle, careful, global process of rulemaking deeply engaged with the public and not merely a scientific consensus.

DECLARATION OF INTERESTS

E.Y.A. serves as co-chair of the Safety Advisory Board of Ohana Biosciences, Inc.

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