American Journal of Law & Medicine (2022), 48: 2-3, 256–265
doi:10.1017/amj.2022.23

American Society of Law, Medicine & Ethics
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ARTICLE

Do Pluripotent Stem Cells Offer a New Path to Reproduction?

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Abstract

The ability of pluripotent stem to develop into any of the cell types in the human body has meant that it was only a matter of time before scientists would try to transform them into human gametes. Up to now though it has not been possible to do so. Nevertheless a 2016 book written by Henry Greely speculated that in twenty to forty years most people in developed countries will cease reproduction through sex, using sex exclusively for pleasure, and instead will rely on reproduction through pluripotent stem cell-derived gametes. This paper will offer a different perspective. After describing the process through which human pluripotent stem cells might eventually be coaxed into gametes, it will show why the use of pluripotent stem cell-derived gametes for reproductive purposes would present significant safety, ethical, and regulatory challenges.

Introduction

Some scientists, lawyers, and ethicists have proposed using pluripotent stem cells as the basis for a new approach to reproduction. This proposed reproductive technology has been given several different names, including pluripotent stem cell-derived gametes (my preference in terminology), in vitro gameteogenesis ("IVG"), and synthetic or artificial embryos. The ability of pluripotent stem cells to develop into any of the cell types in the human body has meant that it was only a matter of time before scientists would try to transform them into human gametes. Successfully doing so would enable scientists to better study the human reproductive process, providing greater insight into the process of gametogenesis and the causes of human infertility. It would also provide new reproductive possibilities for individuals currently unable to have genetically related children and offer a greater range of choice in selecting the characteristics of prospective children. Up until now, scientists have succeeded in developing mouse gametes from pluripotent cells and more recently gametes for some other animal species. There has been some progress but there has not been comparable success with humans. And success with reproductive innovations with animal species such as mice rarely translates directly into success with humans given the significant differences in their reproductive systems.

Nevertheless, Henry Greely speculates in his 2016 book, *The End of Sex and the Future of Reproduction*, that in twenty to forty years, many—perhaps most—people in developed countries will cease reproduction through sex, using sex exclusively for pleasure, and instead will rely on reproduction through pluripotent stem cell-derived gametes.[1] This paper offers a critical analysis of that possibility. While forms of sexless reproduction are presently in use (for example, in-vitro fertilization ("IVF") and artificial insemination) utilizing pluripotent stem cell-derived gametes would be much riskier and more ethically problematic than these practices. After assessing scientific progress related to coaxing

[1] Henry T. Greeley, The End of Sex and the Future of Human Reproduction (2016).

pluripotent stem cells into gametes, this paper discusses why the use of pluripotent stem cell-derived gametes for reproductive purposes would present significant safety, ethical, and regulatory challenges.

Human pluripotent stem cells

In 1998, a scientist at the University of Wisconsin named James Thomson was able, for the first time in U.S. history, to successfully isolate and culture human embryonic stem cells from three- to five-day old human embryos (technically called blastocysts). Thomson's was an important accomplishment because in contrast to adult stem cells—the specialized cells involved in regenerating tissues and repairing damage—these embryonic stem cells are pluripotent. Pluripotency is the ability to generate all cell types and tissues in the human body. Most adult stem cells are confined to reproducing their lineage of origin.

In addition to their pluripotency, embryonic stem cells can also self-renew without losing their genetic structure, can multiply rapidly, and can persist in culture indefinitely. Cell scientists and many others in the scientific and medical communities quickly realized that human embryonic stem cell research held enormous potential: both for contributing to the understanding of the fundamentals of human biology and for developing therapies for many types of incurable diseases. However, because the derivation of embryonic stem cells involved the destruction of three- to five-day-old human embryos, those who accord the embryo high moral status objected, and continue to object, to this line of research.[2]

Another significant step in the development of human pluripotent stem cells occurred in 2006 when a Japanese scientist, Shinya Yamanaka, discovered a way to reprogram specialized adult cells to turn them into the equivalent of earlier-stage stem cells with many of the characteristics of embryonic stem cells. The next year, Yamanaka and Thomson were able, while working separately, to apply this methodology to reprogram human adult cells. Like human embryonic stem cells, these induced pluripotent stem cells—as named by "Shinya Yamanaka" after their discoverery—are pluripotent and capable of differentiating into all cell types, but they do so less efficiently than embryonic stem cells and have some problematic features. Human induced pluripotent stem cell derivatives have been shown to have far more mutations and alterations than human embryonic stem cells, some from the adult cells from which they are derived, because some cells develop mutations as they ageand others from the process of derivation.[3] The high rate of mutations among these derivative cells raises questions about the appropriateness of human induced pluripotent stem cells being used for clinical applications, most particularly as the basis for a reproductive technology. Nevertheless, research proceeds, and some clinical trials for therapies utilizing induced stem cell-based therapies have been put into motion.

Developing gametes from human induced pluripotent stem cells would likely be the more attractive option for prospective parents than would be deriving gametes from human embryonic stem cells. Development using human induced pluripotent stem cells would enable scientists to develop gametes from the somatic cells of prospective parents, thereby establishing a genetic link between the gamete and prospective parents. In contrast, human embryonic stem cells carry the genes of the cells from the embryo from which they were derived, unless they are generated through reproductive cloning, which entails a very arduous and unreliable process. Greely, whose book anticipates a future in which most couples in developed countries opting for sexless reproduction, acknowledges that his predicted scenario would likely depend on the ability to use human induced pluripotent stem cells derived gametes or some other method of creating stem cells derived from prospective parents' own genetic material.[4]

[2]For more on the development of human embryonic stem cells and the controversy generated see A.R. Chapman, *The Ethical Challenges of the Stem Cell Revolution* (Newcastle upon Tyne, UK: Cambridge Scholars Publishing, 2020), Chapter 1.

[3]L.C. Laurent et al., *Dynamic Changes in the Copy Number of Pluripotency and Cell Proliferation Genes in Human ESCs and iPSCs During Reprogramming and Time in Culture*, Cell Stem Cell 106-18 (2011); Liang & Y. Zhang, *Genetic and Epigenetic Variations in iPSCs During Reprogramming and Time in Culture: Potential Causes and Implications for Applications*, Cell Stem Cell 149-59 (2013).

[4]Greeley, *supra* note 1, at 127.

https://doi.org/10.1017/amj.2022.23 Published online by Cambridge University Press

Potential applications of pluripotent derived stem cell-derived gametes

Primordial germ cells go through a multi-stage process to generate spermatozoa and oocytes. Practical and ethical constraints associated with procuring early-stage human gametes have presented significant obstacles to addressing questions about the role of specific genes in early germ cell development and the interactions between germ cells and somatic cells. This knowledge would be relevant to preventing and treating infertility, genetic disease, and some cancers.[5] If the pathway to development of gametes reflects the process through which natural gametes travel, pluripotent stem cell-derived gametes could provide a valuable research tool to gain a better understanding of the mechanisms of gamete development, including the processes of imprint erasure, imprint resetting, and meiosis about which relatively little is known. The availability of pluripotent stem cell-derived gametes could also provide a plentiful supply of embryonic germ cells for scientific research.

The ability to derive human eggs in vitro would also reduce the need to solicit women to donate eggs for research purposes and save them from the health risks related to ovarian stimulation and egg extraction. The fertility drugs used for this purpose can cause side effects such as bloating, abdominal pain, and mood swings, and possibly result in a serious condition termed ovarian hyperstimulation. Ovarian hyperstimulation can cause severe abdominal pain, bloating, nausea, vomiting, and impaired kidney function.[6]

If successfully derived and if successfully shown to be safe for use—two big "ifs" that seem unlikely to occur, at least in the short-term future—pluripotent stem cell-derived gametes could also provide a means to treat infertility problems. Infertility is a clinical condition that affects an estimated 15 percent of heterosexual couples of reproductive age.[7] Individuals may be unable to produce gametes naturally due to organ deficiencies, disease, injuries, or cancer treatments and therefore are rendered unable to have genetically related children. Moreover, assisted reproductive technology techniques are not successful for an estimated 30 percent of infertile patients. Currently, although most prospective parents would much prefer having a genetically related child, the only option for many infertile couples is to adopt a child or to use donated gametes.[8] Some analysts anticipate that pluripotent stem cell-derived gametes could democratize reproduction by making options widely available, while others simply note that stem cell-derived gametes could end infertility.[9] Some have also observed that if pluripotent stem cell-derived gametes are successfully developed and deemed safe to use, some persons who are not infertile might also want to use this technology.[10] But many scientific hurdles must be surmounted before such usage could occur: hurdles related to the successful derivation of pluripotent stem cell based gametes and to the elimination of the errors and mutations to which pluripotent stem cells are prone, particularly induced pluripotent stem cells.

Additionally, Greeley predicts that utilizing pluripotent stem cell-derived gametes could provide prospective parents with a wider range of choice through enabling them to select medical and physical traits for their future children. He describes a reproductive process he terms "Easy PGD," in which advances in genetic knowledge facilitate cheap, accurate, and fast sequencing of the entire genome of an embryo, and an increased understanding of how versions of that sequence would translate into the disease risks, physical characteristics, behaviors, and other traits of the child into which a particular embryo would develop. In his scenario, prospective parents with the financial means to do so would create hundreds or perhaps even thousands of embryos, have them sequenced, eliminate the embryos potentially affected by disease, and then select for implantation the embryo(s) with the traits most attractive to them.[11] However, it is unlikely that PGD would ever be able to provide the detailed

[5]Hinxton Group, Consensus Statement: Science, Ethics and Policy Challenges of Pluripotent Stem Cell-Derived Gametes 2 (2008) https://www.hinxtongroup.org/au_pscdg_cs.html.

[6]Inmaculada de Melo-Martín: Rethinking Reprogenetics: Enhancing Ethical Analysis of Reprogenetic Technologies 170 (2016).

[7]Inmaculada Moreno et al., *Artificial Gametes from Stem Cells*, 33 CERM (2015).

[8]Junaid Kashir et al., *Viability Assessment for Artificial Gametes: The Need for Biomarkers of Functional Competency*, Biology of Reproduction 1 (2012).

[9]Anna Smajdor & Daniella Cutas, *Artificial Gametes*, Nuffield Council on Bioethics, 1, 9 (2016) https://www.nuffieldbioethics.org/wp-content/uploads/Background-paper-Artificial-gametes.pdf.

[10]Kashir et al., *supra* note 8, at 3.

[11]Greely, *supra* note 1, at 150-52.

https://doi.org/10.1017/amj.2022.23 Published online by Cambridge University Press

information Greely envisions, because many of the traits of greatest interest to prospective parents are not shaped by single genes but by a network of genes, each making a small contribution.

Moreover, some ethicists and legal analysts take issue with Greely's belief that providing couples with such a broad range of reproductive choice would be advantageous. For example, Sonia Suter has written about the enormous challenges to reproductive decision-making that would result from the capacity to create extensive numbers of embryos for which prospective parents might then obtain extensive predictive information. Suter theorizes that the dizzying amount of predictive information about the health and traits of potential future children that would be made available, and the attempt to choose embryos with the "best" combination of genetic variants, could overwhelm future parents. She cautions that this innovation has the potential to result in choice overload and paralysis.[12] That seems to be a likely outcome of "Easy PGD" should it ever become a reality.

Scientific progress in developing gametes from pluripotent stem cells

Germ cells are difficult to generate from pluripotent stem cells due to the number of growth stages through which they pass and the complex differentiation process—meiosis—which requires them to divide to have half the chromosomes of other cells. Nevertheless, there has been progress toward development of pluripotent stem cell-derived gametes from research with mice and recently with macaque monkeys but less so with the development of human gametes from pluripotent stem cells. In evaluating the development of stem cell-derived gametes, it is important to note that differences between human and mouse stem cells mean that advances in murine research do not translate directly into human applications. Mouse embryonic stem cells are "naïve," meaning they are easy to coax into differentiation paths, whereas human stem cells are "primed" in a way that makes them less adaptable.[13] Also, the reproductive processes of mice differ from those of humans in key ways. On the other hand, nonhuman primates have primed stem cells, and developing early-stage monkey sperm from stem cells represents a significant step forward.

In 2016, a team of Japanese scientists was able to generate functional male and female mouse germ cells from mouse induced pluripotent stem cells. The oocytes were fertilized through IVF and implanted, and mice pups were born from the oocytes.[14] Several recent papers have described the successful in vitro development of mouse gametes derived from pluripotent stem cells. One group generated functional sperm from mouse embryonic stem cells that mimicked the three essential stages that occur in the testes that were able to fertilize an egg and then create embryos that resulted in viable fertile offspring.[15] In another experiment, mouse egg cells were made in vitro from both mouse embryonic and induced pluripotent cells by incubating them in mouse ovarian follicular tissue. The mouse egg cells then generated live mice through IVF.[16] Other scientists in 2021 were able to use rhesus macaque embryonic stem cells to generate sperm cells in the earliest stage of development. Rhesus macaques have a more similar reproductive system to humans than do mice.[17]

Preliminary efforts to develop human pluripotent stem cell–derived gametes are taking shape. In 2014, an Israeli and UK research team developed human primordial germ cells, using human embryonic stem cells. Primordial germ cells appear very early in embryo formation and go on to become egg and sperm.[18] In

[12]Sonia M. Suter, *The Tyranny of Choice: Reproductive Selection in the Future*, 5 J. Law Biosci. 262, 265 (2016).

[13]David Cyranoski, *Rudimentary Egg and Sperm Cells Made from Stem Cells,* Nature 1, 2 (2014).

[14]David Cyranoski, *Mouse eggs made from skin cells in a dish*, Nature (2016).

[15]Orie Hikabe et al., *Reconstitution in vitro of the entire cycle of the mouse female germ line*, Nature 299-303 (2016).

[16]Takashi Yoshino et al., *Generation of ovarian follicles from mouse pluripotent stem cells*, Sci, July 2021 at 282-90.

[17]Sujittra Khampang et al., *Blastocyst Developed after Fertilisation with Invitro Spermatids from non-Human Primate Embryonic Stem Cells*, 2 Fertility & Sterility Sci., 365, 366 (2021).

[18]Naoko Irie et al., *SOX17 Is a Critical Specifier of Human Primordial Cell Fate*, 160, Cell 253, 253 (2015); D. Cyranoski, *Rudimentary Egg and Sperm Cells Made from Stem Cells,* Nature, (Dec. 24, 2014) https://www.nature.com/articles/nature.2014.16636.pdf.

https://doi.org/10.1017/amj.2022.23 Published online by Cambridge University Press

2018, a team of Japanese scientists turned human blood cells into stem cellsand then into cells closely resembling human oogonia, an intermediate embryonic precursor for human oocytes. While an important feat, the oogonia, which were produced in mouse ovaries, were too immature to be fertilized to create an embryo.[19] Hence, human pluripotent stem cells have been induced into primordial germ-like cells, but further development into mature germ cells has not yet been achieved.

Safety issues

Safety is a critical factor when evaluating whether to adopt any new medical therapy, and it is especially vital for a new reproductive technology that would potentially affect not only the immediate child but future generations, as well. The welfare of the child and of future generations of children, rather than the preferences of prospective parents, should be the paramount consideration in determining whether a new reproductive therapy or technology should be adopted. As such, the assessment of any new reproductive technology requires proceeding with extreme caution in order to protect the well-being of a future child. The potential damage to the child could be serious and irreversible, and therefore the onus to prove that the proposed technology is safe should be on the researchers developing pluripotent stem cell-derived gametes and the regulatory agencies evaluating them.

Thus, consideration of the clinical use of pluripotent stem cell–derived gametes should depend on the ability to identify and address its long-term and multi-generational consequences for the child(ren) who will be born through this technology to assure that it poses little risk over existing, less risky alternatives. Clinical use of pluripotent stem cell-derived gametes poses many potential risks. Children conceived through stem cell-derived gametes might suffer serious genetic anomalies or health impairments. Even if stem cell-derived gametes resemble functional gametes, they may not be fully normal. For example, the development of an embryo through this technology might be affected by imprinting errors that are not apparent. [20]

A significant problem in assessing risks is the limit on our knowledge about the way gametes develop naturally. Because the mechanisms of differentiation and maturation of spermatozoa and ova have not been fully elucidated, scientists face difficulties in evaluating whether pluripotent derived germ cells have the full functionality of human sperm and eggs. For example, we do not yet understand the implications of switching cell types from a differentiated to an undifferentiated state, or of erasing and resetting imprinting patterns to facilitate reproduction.[21] Additionally, while we can (and should) conduct extensive animal testing for new reproductive technology on large mammals including nonhuman primates, and not just mice which to date have been the primary research model, we cannot assume that what works without complications or heightened risks in one species will work similarly in humans, given the significant differences between different species' reproductive systems.

With safety considerations in mind, it is concerning that gametes derived from human induced pluripotent stem cells (iPSCs) would likely be preferred by prospective parents over gametes derived from human embryonic stem cells, because these gametes would enable prospective parents to have a genetic link with their future offspring if the pluripotent stem cells were derived from one of their body's cells. In contrast, gametes generated from embryonic stem cells would contain the genes of the embryo from which it was derived. As mentioned above, induced pluripotent stem cells have been shown to have far more abnormalities than human embryonic stem cells, some generating from the adult stem cells from which they are derived and others induced by the derivation process used to produce the cells. Neither abnormality risk would be easily managed. All adult cells have some mutations in them, and it is unlikely the derivation process for induced pluripotent stem cells can be fundamentally changed.

[19]C. Yamashirobuta et al., *Generation of Human Oogonia from Induced Pluripotent Stem Cells in vitro*, Sci, Oct. 2018, at 356.
[20]Smajdor & Cutas, *supra* note 9, at 12.
[21]Sonia M. Suter, *In Vitro Gametogenesis: Just Another Way to Have a Baby*, 3 J. of L. & the Biosciences 87, 89 (2016).

https://doi.org/10.1017/amj.2022.23 Published online by Cambridge University Press

Gene editing technology like CRISPR/Cas 9 might eventually offer a solution, but there is currently a consensus that off-target side effects and risks of unforeseen undesirable effects threaten the prudence of proceeding with heritable genome editing of pluripotent stem cells. The central recommendation in the study report on the subject, prepared by an expert committee on behalf of the U.S. National Academy of Medicine, the National Academy of Sciences, and The Royal Society, states that "[n]o attempt to establish a pregnancy with a human embryo that has undergone genome editing should proceed unless and until it has been clearly established that it is possible to efficiently and reliably make precise genomic changes without undesired changes in human embryos. These criteria have not yet been met…"[22]

Sutter points out that ultimately, all new reproductive technologies must proceed to clinical applications in order to move forward. Accordingly, the only way to demonstrate the effectiveness and safety of this technology in humans will be to use pluripotent stem cell-derived gametes in a clinical setting to test whether they can indeed produce viable offspring. Deciding if and when to move forward with such clinical applications may be one of the biggest obstacles to the testing and adoption of this technology. Sutter comments that had we subjected IVF to the kind of regulations and oversight requirements currently in place for reproductive technology, it might never have been adopted.[23] Yet the stakes of moving forward with a high-risk reproductive technology render loosening those standards unjustifiable.

Greely raises a number of issues that the U.S. Food and Drug Administration ("FDA") will need to resolve if it grants approval to such clinical applications (as Greely anticipates that it will). How long should the trials run? Until the babies are born, until they are of a certain age (and if, so how old)? Until they are adults who have themselves reproduced? Greely also questions who will fund these trials and who will accept the risks and liability of problems should they occur. He additionally wonders how, if the trials were to get approved and funded, the FDA should evaluate these data and determine that making babies from iPSC derived gametes is safe and effective.[24] Resolving these issues will prove difficult.

There is also a risk that, even if the use of stem cell-derived gametes is not proven to be safe and does not get the approval of the FDA or a comparable regulatory agency elsewhere, the technology may nevertheless be used. There is a history of reproductive technologies being introduced by the little regulated fertility industry in the United States without careful research to assess their safety.[25] Some unscrupulous fertility centers may be willing to offer patients the technology if it is developed, particularly by the predominantly for-profit fertility centers in the United States. The 2016 case of a New York based clinic taking one of its patients to Mexico to treat her with an untested and unapproved mitochondrial replacement technique and then advertising its availability on their website constitutes one such example.[26] He Jiankui's 2018 genetic editing experiment on the embryos of twin girls, which were then implanted and brought to term, also shows the danger of rogue scientists, desirous of achieving a major breakthrough and the notoriety of doing so, proceeding with reproductive experiments without the technology being evaluated for safety or authorized by the relevant oversight agency.

In weighing the risks against the benefits of the use of stem cell-derived gametes for reproductive purposes, it is important to remember that there are other, less risky paths to parenthood for persons with reproductive limitations, such as the adoption of children and the use of donor gametes. Both of these options, however, have the drawback of not providing a genetic linkage between the parent(s) and the child. But, as Immaculada de Melo-Martin argues, satisfying the desire to have a genetically related offspring should not constitute a scientific priority, given the many other pressing needs that exist.[27] The

[22]Int'l Comm'n on the Clinical Use of Hum. Germline Genome Editing et al., Heritable Human Genome Editing 3 (2020).
[23]Suter, *supra* note 21, at 97-98.
[24]Greely, *supra* note 1, at 218-222.
[25]W. Dondorp & G. De Wert, *Innovative reproductive technologies: risks and responsibilities*, 26 Human Reproduction 1604, 1605 (2011).
[26]Jennifer Couzin-Frankel, *Unanswered Questions Surround Baby Born to Three Parents*, *News*, Science (Sept. 27, 2016), https://www.science.org/content/article/unanswered-questions-surround-baby-born-three-parents.
[27]de Melo-Martin, *supra* note 6, at 265.

https://doi.org/10.1017/amj.2022.23 Published online by Cambridge University Press

Nuffield Council on Bioethics also questions the extent to which it is justified to invest in the development of pluripotent stem cell–derived gametes, given the risks and costs involved and the availability of alternatives to genetic disorders. Preimplantation genetic diagnosis (PGD) can screen for chromosomal abnormalities and genetic mutations in a developing oocyte or embryo before transfer into a woman's body to enable the selection of a healthy embryo and to preserve a genetic relationship between prospective parents and the child.

So how far have we progressed in determining the safety of human pluripotent stem cell-derived gametes? The 2021 Guidelines of the International Stem Cell Research Committee (ISSCR), the leading international body of stem cell scientists and ethicists, recommended that basic research with human pluripotent stem cell-derived gametes was permissible with careful oversight by an expert committee of scientists and ethicists. But the Guidelines placed implantation of stem cell-derived gametes into a human uterus in its category of currently prohibited activities. The Guidelines also warn that experiments involving the transfer of a pluripotent stem cell-derived embryo into the uterus of a nonhuman host should also not be pursued, due to the broad scientific consensus that such experiments lack a compelling scientific rationale and are widely considered to be unethical. Research and applications in this category are currently deemed to be unsafe and raise unresolved ethical issues.[28] According to the Guidelines, "there is no compelling scientific evidence that IVG (in vitro gametogenesis) is currently safe for use in human reproduction, particularly when starting with hESCs (human embryonic stem cells), iPSCs (induced pluripotent stem cells), or iPSC derivatives."[29] These reservations owe to unresolved scientific issues, and the reportedly lower quality of mouse oocytes and primordial germ cells derived from stem cells compared to their in vivo counterparts.[30] The lower quality of mouse oocytes and primordial germ cells derived from stem cells than their in vivo counterparts is a difficult obstacle to surmount. But these recommendations are subject to reconsideration and modification.

Ethical issues[31]

The only way to determine the functionality of pluripotent stem cell–derived gametes, and to establish their capacity for fertilization and early embryogenesis, will be to use them to create embryos through in vitro fertilization. Pluripotent stem cell-derived oocytes will need to undergo functional tests using natural sperm to assess whether fertilization can occur, and doing so will create embryos. Pluripotent stem cell-derived sperm will have the same requirement with oocytes. The creation and destruction of large numbers of embryos during this experimentation is likely to pose ethical problems for many, more so than the numbers of embryos created and stored from IVF because these embryos are considered to be potential babies. The likely scale of the numbers of embryos created and destroyed to develop and test pluripotent stem cell-derived gametes may even breathe new life into the specter of "embryo farming" and exacerbate concerns about scientific research devaluing human life.[32] Even those who do not imbue the human embryo with full human status may still have moral qualms about such an instrumental treatment of human life and concerns regarding the impact destroying large numbers of embryos will have on the commitment to the sanctity of human life.[33]

Another issue is how long it will be scientifically necessary to allow these embryos to develop before destroying them in order to determine their functionality. Beyond evaluating their capacity for fertilization, it will be important to examine whether these research embryos develop normal body

[28]Amander T. Clark et. al., *Human embryo research, stem cell-derived embryo models and in vitro gametogenesis: Considerations leading to the revised ISSCR guidelines*, 16 Stem Cell Reports 1416, 1421 (2021).

[29]*Id.* at 1421.

[30]*Id.* at 1422.

[31]Parts of this section of the paper are based on Chapter 7 in Chapman, *supra* note 2, at 149-69.

[32]I. Glenn Cohen, George Daley & Eli Adashi, *Disruptive Reproductive Technologies*, 9 Sci. Transl. Med. (2017).

[33]Ronald Green, The Human Embryo Research Debates: Bioethics in the Vortex of Controversy 79.

https://doi.org/10.1017/amj.2022.23 Published online by Cambridge University Press

plans and germ layer formation when compared with embryos developed from natural eggs and sperm. Doing so may require maintaining research embryos in vitro beyond the current 14-day limit.[34] The permissibility of extending this observation period will depend on whether the current debate about extending embryos in culture for research purposes beyond the current 14-day rule results in the loosening of this standard. Although both the creation and destruction of embryos for testing the viability of pluripotent stem cell-derived gametes and the maintenance of the embryos in culture beyond 14 days pose ethical issues proceeding with the development of pluripotent stem cell-derived gametes for potential clinical use without these precautions would risk the introduction of a technology with significant potential for human harm.

Some analysts also anticipate that pluripotent stem cell-derived gametes could be used for germ line inheritable genetic modification to correct disease mutations, introduce disease resistance, or facilitate other biological enhancement.[35] Such enhancements would raise other ethical issues, as have proposals for enhancement with other technologies. Pluripotent stem cell-derived gametes offer two potential approaches to enhancement. One is to screen and alter the gametes before implantation using gene editing techniques such as CRISPR/Cas 9. The second would be for prospective parents to have many stem cell–derived gametes made, use PGD to screen the embryos using these gametes, and then select among them to try to have a child without genetic problems (however the phrase "genetic problem" is defined) and with the traits they desire. This is the scenario portrayed in the 1997 movie "Gattaca" in which "improved" persons born through a similar process of genetic selection have higher social status and more life opportunities than those born through natural means.

If Greely's proposed "Easy PGD" process" were to become clinically viable, it would provide for this latter type of selection. He postulates that science will be able to perfect this technology in twenty to forty years.[36] I have strong doubts. Greely is not very concerned about the implications of enhancements through "Easy PGD" because "Easy PGD" would only be able to select among the genetic variants already present in prospective parents. He anticipates it would result in no more than a 10 to 20 percent healthier, better looking, and smarter children.[37] A 10 to 20 percent improvement might not be as insignificant as Greely indicates. Moreover, if "Easy PGD" were to become a reality and growing numbers of people were to engage in it, over generations the practice could also result in considerably more than a10 to 20 percent improvement.

Moreover, as has been pointed out, the introduction of potential enhancements from any reproductive technology would likely exacerbate social inequalities, because those most likely to take advantage and able to afford the treatments would be white, economically well-off couples—the same people who are currently the predominant users of reproductive technologies.[38] This would enable those with the most resources to add to the many advantages their children already have. It could also magnify the differences between various countries' populations, depending on how many in their populations have access to these technologies.

Importantly, the fundamental questions regarding the ethics of enhancing future children with heritable changes have not been resolved. Many view efforts to do so as crossing an ethically inviolate line. Before proceeding in that direction, there would need to be meaningful discussions to reach a decision about the ethics of potential enhancement applications that involved a broader cross-section of the population than a single researcher or a small group of experts. As a caution, the 2017 international panel convened by the National Academy of Science approved the use of gene therapy and gene editing

[34]Annalien Bredenoord & Insoo Hyun, *Ethics of Stem Cell-derived Gametes Made in a Dish: Fertility for Everyone?* 9 EMBO Mol. Med. 396, 396 (2017).

[35]Guido de Wert et al., *Responsible Innovation in Human Germline Gene Editing: Background Document to the Recommendations of ESHG and ESHRE*, 26 Eur. J. of Human. Gen. 450, 459 (2018).

[36]Greely, *supra* note 1, at 133.

[37]*Id.* at 238-40.

[38]de Melo-Martin, *supra* note 6, at 15.

https://doi.org/10.1017/amj.2022.23 Published online by Cambridge University Press

for somatic applications under carefully defined circumstances, but it recommended that genome editing for enhancement purposes not be allowed.[39]

Another issue is the potential impact that the application of this technology would have on our conception of parentage, as is the psychological impact that using stem cell-derived gametes could have on children born as a result. Simply put, the adoption of a technology that alters the reproductive process in this way could also fundamentally change the relationship between parents and their children. Would the use of engineered stem cell-derived gametes increase parental control of the destiny of their children in a problematic way? Greely discusses how genetically selected children would feel knowing that their parents selected them with more than the usual hope of the child having specific physical, behavioral, and cosmetic traits. He points out that these questions are not entirely unprecedented since prospective parents can already use technologies giving them some of the same choices.[40] He also dismisses those ethicists who have raised questions about children's rights to an open future. I think the psychological impact could be greater than Greely anticipates given how much control "Easy PGD" would confer on prospective parents. Moreover, I think he dismisses the right of children to have major choices about their futures too cavalierly.

The adoption of pluripotent stem cell-derived gametes would also raise questions about who the true parents would be – the source of the biological materials used in deriving the gametes, or the person gestating them? What would it mean psychologically for a child born through gametes developed from embryonic stem cells to learn that her progenitor had never lived and was destroyed in the process of her creation? [41] Would it psychologically harm a child to learn that a parent's skin cells technically were the founding material for her life?

Conclusion

This paper assesses the possibility of using pluripotent stem cells as the basis for a new reproductive technology. As noted, there are many scientific hurdles both to develop pluripotent stem cell gametes and to assess the risks of harm their use would pose to the children potentially born from them and their descendants. Given that the differentiation and maturation mechanisms of spermatozoa and ova have not been fully elucidated, it is possible that pluripotent derived germ cells may not have the full functionality or quality standards of human sperm and eggs. Importantly, ISSCR decided that "there is currently no compelling scientific evidence that stem cell-derived gametes are currently safe for use in human reproduction particularly when starting with human embryonic stem cells, induced pluripotent stem cell like cells, or induced pluripotent stem cell derivatives." This assessment reflected unresolved issues related to epigenetic and genetic abnormalities of the resulting gametes from murine experiments and the discovery that mouse oocytes and mouse primordial germ cell like cells developed from pluripotent stem cells were reported to be of lower quality than their in vivo counterparts.[42] Moreover, future animal trials, even with nonhuman primates, cannot provide conclusive evidence of safety in humans. And it is important to remember that the negative impact would not only be limited to the persons born in one generation. It is particularly concerning that induced pluripotent stem cells, which likely would be preferred by prospective parents desirous of having a genetic link with their offspring, have intrinsic problems that appear to render them inappropriate for reproductive purposes.

However, the further development of such gametes could be beneficial. Gametes developed from pluripotent stem cells might offer a new model for studying gamete formation and the fertilization process and by doing so could potentially help identify the causes and contribute to the treatment of fertility problems. For these reasons it is appropriate to go forward with the research on the development

[39]Commission on Human Gene Editing, *supra* note 22.
[40]Greely, *supra* note 1, at 228.
[41]Smajdor & Cutas, *supra* note 9.
[42]Clark et al., *supra* note 27, at 6-7.

https://doi.org/10.1017/amj.2022.23 Published online by Cambridge University Press

of the gametes. The 2021 ISSCR Guidelines recommended that basic research to develop human pluripotent stem cell gametes should be allowed but not experiments designed to fertilize the gametes.[43] I would agree with the addition of a further stipulation that such research only take place in an institutional setting where the regulatory process can assure that the research is monitored carefully to prevent fertilization and implantation.

Further scientific research and analysis will be required to determine the balance between the risks and benefits of other types of research with human pluripotent stem cell gametes, and there is a need to be cautious in the interim. The dilemma will be how to make such assessments and to determine what level of risk will be deemed acceptable. Clearly this is not a decision that scientists should make on their own. It needs extensive societal deliberations.

An article by Eli Adashi, I. Glenn Cohen, and colleagues notes that the implications of scientific breakthroughs are rarely addressed in advance of their realization. The authors call for the conduct of thoughtful *ante hoc* deliberations on the prospect of developing pluripotent stem cell-derived human gametes, which they characterize as a disruptive technology in waiting. Their goal is to minimize potential untoward *post hoc* regulations. They have in mind the model the British Human Fertilisation and Embryology Authority used to decide whether to approve mitochondria replacement applications.[44] I would agree that the prospect of developing and using pluripotent stem cell-derived gametes would suggest the need to begin *ante hoc* deliberations, but in my case it would be for the purpose of deciding what kinds of regulations and statutory provisions would be required to proceed cautiously and to limit the unauthorized uses of pluripotent stem cell-derived gametes for human reproductive applications.

Clearly, pluripotent stem cell-derived gametes do not currently offer a new path for human reproduction, and they may never do so. I am less optimistic than the 2021 ISSCR Guidelines appear to be in their assessment that pluripotent derived stem cells are a promising technology for the future once the ethical and scientific issues related to them are resolved.[45] As future decisions are made about the use of pluripotent stem cell-derived gametes it will be important to be cautious and aware that these decisions have import for future generations.

[43] *Id.* at 6.

[44] Eli Adashi et al., *Stem Cell-Derived Human Gametes: The Public Engagement Imperative*, 25 Trends in Mol. Med. 165, 165-67 (2019).

[45] Clark et al., *supra* note 28, at 8.

Cite this article: Chapman, A.R. (2022), 'Do Pluripotent Stem Cells Offer a New Path to Reproduction?', *American Journal of Law & Medicine*, **48**, pp. 256–265. https://doi.org/10.1017/amj.2022.23