RETHINKING GENERAL CONSENT FOR STEM CELL-BASED EMBRYO MODEL RESEARCH

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Advances in stem cell research now allow us to create embryo models outside the womb with stem cells originally derived from human skin. The models provide novel opportunities to understand human development, fertility, and genetics, yet bring potential ethical and legal challenges. Current ethical and legal work centers on the moral status of embryo models, but no one has evaluated the complexity this new research adds to the relationship between researchers and biological material donors or between donors and the research itself. I argue the use of previously collected biological material for stem cell-based embryo models opens novel ethical and legal concerns. Broad consent models take autonomy away from research participants in a controversial area of research. Current common law property doctrine would not apply easily to a dispute over stem cell-based embryo models, and current statutes do not protect aggrieved research participants. This Note outlines an informed consent structure for stem cell-based embryo model research that considers both research participant autonomy and possibilities for future innovation. I advocate for researchers to apply dynamic consent in their research by collecting new biological material and investing in continued relationships with donors.

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INTRODUCTION

"The day is here - we made babies from only skin cells!"[1] Imagine a world where this headline pops up on your phone, tablet, or computer. What does it mean? How is this possible? What do we do about it? While a stem cell-derived baby is not yet a scientific reality, scientists have created what may well be early-stage human embryos with stem cells derived from human skin.[2] Scientists have not yet tried to use stem cell-based embryo models to produce a baby.[3] Instead they use the models to better understand early embryonic human development, genetics, fertility, and disease progression.[4]

The creation of babies from the skin cells of unknowing donors raises ethical and legal concerns about bodily autonomy and parenthood. Even before new methods are used to create living human beings, current embryo model technology raises novel concerns about biomedical research law, regulation, and ethics. Research has already advanced far enough that it no longer fits squarely into established informed consent and property doctrines. The work of reputable and well-meaning scientists sits in gray areas, raising the need for regulatory attention.[5] Moreover, clear regulation is important because social and political outcry

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1 *See* Kelly Murray, *Could we one day make babies from only skin cells?*, CNN (Feb. 9, 2017, 10:58 AM), https://perma.cc/42XW-BJ3H (discussing the potential for in vitro gametogenesis, the process of making egg and sperm from induced pluripotent stem cells derived from skin cells).

2 *See* Leqian Yu et al., *Blastocyst-Like Structures Generated from Human Pluripotent Stem Cells,* 591 NATURE 620 (2021).

3 Stem cell-based embryo models go by a number of names in scientific, ethical, and legal literature. Naming ranges widely from "embryo model" to "embryoid" to "synthetic human entities with embryo-like features." Ethics scholars have recognized the need for consistency. Nicolas et al. recommends using the term "embryoid" but to also refer to embryoids modeling specific phases of development according to the stage such as gastruloid, *see* Paola Nicolas et al., *The Ethics of Human-Embryoids Model: A Call for Consistency*, 99 J. OF MOLECULAR MED. 569, 569-71 (2021). In this Note, I have decided to use the naming scheme recommended by the 2021 International Society for Stem Cell Research (ISSCR) guidelines. As the ISSCR guidelines are the most comprehensive recommendations, the choice allows me to map examples to the guidelines. *See* 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 REP. 1416, 1418-19 (2021) ("In addition, to best reflect the state and the envisioned applications of these structures made from stem cells, the use of the umbrella term 'embryo model' or 'stem cell based embryo model' is encouraged, while the use of the term 'synthetic embryo' or 'artificial embryo' or 'embryoids' should be avoided.").

4 *See* Jianping Fu et al., *Stem-Cell-Based Embryo Models For Fundamental Research and Translation,* 20 NATURE MATERIALS 132, 134 (2021); *see also* Nicolas Rivron et al., Comment, *Debate Ethics of Embryo Models from Stem Cells,* 564 NATURE 183, 184 (2018).

5 Regulations and policy have largely reacted to cases that the public sees as scientific oversteps or when scientific research contributes to unreasonable harm. For example, informed consent principles that are outlined in the Belmont Report and codified in American law resulted in part from publicization of the horrific experiments Nazi scientists conducted without consent and the class-action lawsuit brought against the Public Health Service on behalf of

has previously halted important research progressions in moral and regulatory gray areas.[6] Such moratoriums on research can stall lifechanging breakthroughs. Preemptive conversation and regulatory action can prevent unnecessary bans.

In beginning to grapple with issues surrounding stem cell-based embryo model research, scholars have focused on the moral status of the embryo models themselves. By debating what aspects of human embryos should be modeled and how long models should be allowed to develop, scientists and ethicists have opened the important conversation into the legal and ethical implications of stem-cell-based embryo models.[7] These discussions have resulted in recommendations to extend the timeframe when researchers can grow embryos and embryo models outside the womb past the current fourteen-day rule.[8]

Scholars have less frequently focused on how technological advances in stem cell research and embryo models change the relationship scientists have with those who donate biological material.[9] Researchers often use cells previously collected for alternative purposes for stem cell-based embryo research. Because the material was previously collected with broad consent, those performing stem cell-based embryo research risk breaching the ethical and legal standards that have been designed to protect donors. Specifically, researchers potentially

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black men who, despite being told they were in a study on syphilis treatment, were actually enrolled in a study to understand "untreated" syphilis. *See* Kailee Kodama Muscnete, *Ethics and the IRB: The History of the Belmont Report, Teacher's College, Columbia University:* IRB BLOG (Aug. 3, 2020), https://perma.cc/L4KF-ABH3; DEP'T OF HEALTH, EDUC., & WELFARE, OFF. OF THE SECR'Y, Belmont Report (n.d.), https://perma.cc/2NCT-49PH.

6 *See infra* note 17 and accompanying text.

7 *See, e.g.*, John Aach et al., *Addressing the Ethical Issues Raised by Synthetic Human Entities with Embryo-Like Features*, 6 ELIFE (2017); Rivron, *supra* note 4; Tsutomu Sawai et al., *The Moral Status of Human Embryo-Like Structures: Potentiality Matters?*, 21 EMBO REPS (2020).

8 The Ethics Advisory Board of the Department of Health and Human Services proposed a fourteen-day rule for embryo research in 1979. ETHICS ADVISORY BD., DEP'T OF HEALTH, EDUC. & WELFARE, *HEW Support of Research Involving Human In Vitro Fertilization and Embryo Transfer* (1979); The United Kingdom convened an international committee that proposed a similar fourteen-day rule for embryo research in 1984. Mary Warnock, Dep't of Health & Soc. Sec., Report of the Committee of Inquiry into Human Fertilisation and Embryology (Her Majesty's Stationery Office 1984) (U.K.); *see also* Jonathan Tourelle, *Human Fertilisation and Embryology Act (1990)*, Ariz. State Univ.: EMBRYO PROJECT ENCYCLOPEDIA (Dec. 19, 2014), https://perma.cc/63F3-6BG6. The calls to end or extend the 14-day rule reference its lack of a developmental basis and its inability to work well with new in vitro technologies such as stem cell-based embryo models. *See* Aach et al., *supra* note 7 (arguing for abandoning the 14-day rule in favor of a rule based on development of specific features); Nicolas et al., *supra* note 3 (calling for a sliding scale rule that accounts for the completeness of the embryo model rather than a strict 14-day rule); Nidhi Subbaraman, *Limit on Lab-Grown Human Embryos Dropped by Stem-Cell Body*, 594 NATURE 18 (2021) (announcing International Society for Stem Cell Research recommended regulators and national academies of science reevaluate the 14-day rule).

9 *See, e.g.*, Osagie K. Obasogie & Helen Theung, *Moore is Less: Why the Development of Induced Pluripotent Stem Cells Might Radically Upend Property Law Concerning Human Tissues as We Know It*, 16 STAN. TECH. L. REV 51 (2012).

violate informed consent laws that are designed to prevent researchers and physicians from breaching ethical duties including respect for bodily autonomy. The history of controversy around stem cell research and embryo research, tied to the lifelike potential of the models, heightens the risk of backlash from biological material donors or the media. I argue that, rather than waiting for backlash, researchers should preemptively engage with communities who donate cells for stem cell-based embryo model research to ensure donors understand the goals of the research and want to participate.

This Note will proceed in three sections. First, I will provide the necessary scientific and regulatory background to frame the ethical and legal issues that arise when stem cells are used to model human embryos in research. Second, I will present the ethical and legal problems that arise with the development of new embryo models. Third, I will propose a solution to these problems. Throughout these sections, I will reference three recent research papers as case studies.[10]

Ultimately, I propose discarding general consent practices in favor of specific informed consent for embryo model research. By requiring specific consent for research on stem cell-based embryo models at the time new material is collected, scientists can have open conversations with participants about the goals of their work. Researchers should also employ dynamic, continuing consent models when they plan to continue collecting data from new cell lines. These proposed changes will reaffirm research participant autonomy in a morally gray area of research, decrease litigation risk, and prevent judges from facing difficult questions about property law or the legal definition of life.

I. Development and Use of Stem Cell-based Embryo Models and Human Subject Research Guidelines

A. Stem Cell Research Leads to New Models for the Study of Early Development

This Note focuses on a technology called "stem cell-based embryo models." To provide context for the bioethical and legal issues arising from this technology, this section explains the development and use of these models. The following section provides background on stem cells, discusses how embryo development proceeds without technological intervention, and illustrates how scientists use stem cells to create models of embryo development absent fertilization.

10 *See* Yu et al., *supra* note 2; Katherine Rhodes et al., *Human Embryo Bodies as a Novel System for Genomic Studies of Functionally Diverse Cell Types,* 10 eLIFE (2022); Yi Zheng et al., *Controlled Modeling of Human Epiblast and Amnion Development Using Stem Cells,* 573 NATURE 421 (2021).

B. A Brief Scientific and Political History of Stem Cell Research

Most cells in the human body are specialized for one particular function. Such cells either do not regenerate at all or divide a finite number of times before dying. For example, heart muscle cells, called cardiomyocytes, are responsible for generating the contracting motion of a heartbeat.[11] After birth, cardiomyocytes do not divide to generate new heart cells.[12] If all cells of the body acted like cardiomyocytes, we would need to be born with all the cells that our body needs in our lifetime.

Our bodies, however, contain cells called stem cells that continue to divide, regenerate, and specialize throughout our lifetimes. These non-specialized, immature cells divide to become more specialized cell types (like cardiomyocytes).[13] Stem cells have the unique property of "pluripotency" – they can divide to regenerate themselves as well as specialize into any other cell type in the human body.[14] Differentiation is the process by which stem cells divide to become more specialized cell types.[15]

The possibility of isolating human stem cells opened novel opportunities for studying the human body and for regenerative medicine. As a result, scientists quickly began research to differentiate human stem cells (hESCs) into cell types not easily accessible for research, and clinical researchers explored the possibility of using human stem cells-derived tissues for transplantation.[16] Yet, soon after, stem cell research quickly became a political issue because the isolation of hESCs required destruction of early-stage human embryos. In 2001, President

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11 This is the conventional thought, but though there is some evidence of cardiomyocyte turnover in adults, heart growth is more likely due to an increase in cardiomyocyte size. *Compare* Preeti Ahuja et al., *Cardiac Myocyte Cell Cycle Control in Development, Disease, and Regeneration*, 87 PHYSIOLOGICAL REVS. 521, 522 (2007) ("Cardiac myocytes rapidly proliferate during fetal life but lose their ability to proliferate soon after birth.") *with* Thomas Eschenhagen et al., *Cardiomyocyte Regeneration A Consensus Statement*, 136 CIRCULATION 680, 680-82 (2017).

12 Elizabeth A. Woodcock & Scot J. Matkovich, *Cardiomyocytes Structure, Function and Associated Pathologies*, 37 INT'L J. BIOCHEMISTRY & CELL BIOLOGY 1746, 1747 (2005).

13 Mayo Clinic Staff, *Stem Cells: What They Are and What They Do*, MAYO CLINIC (Mar. 19, 2022), https://perma.cc/3HXF-6SLW.

14 This is a simplified discussion of stem cells. In this Note when I refer to stem cells, I am referring to pluripotent stem cells that can only be found naturally in the inner cell mass of early embryos. (I will also explain in the next section how scientists have identified ways to create pluripotent stem cells from other human tissue) There are multiple types of "stem cells," including those that do not have full pluripotency. Adult bodies contain stem cells that help to regenerate some adult tissues. These cells are multipotent, meaning they can differentiate into some, but not all, cell lineages. For example, hematopoietic stem cells are blood cells that produce new blood and immune cell types, *see* Malek J. Los et al., *Stem Cells*, in Stem Cells & Biomaterials for Regenerative Medicine 5, 5-13 (Marek J. Łos, Andrzej Hudecki & Emilia Wiecheć, eds., 2019), https://perma.cc/7729-78AW.

15 Mayo Clinic Staff, *supra* note 13.

16 *See* HENRY T. GREELY, THE END OF SEX AND THE FUTURE OF HUMAN REPRODUCTION 94 (2016).

George W. Bush responded to the outcry by severely limiting research funding for hESCs – and thus limiting the potential for innovation in the space.[17]

A turning point for stem cell research came in 2007 when Shinya Yamanaka announced a world-changing breakthrough, human induced pluripotent stem cells (iPSCs).[18] His team had developed hESC-like cells that could be cultured in the lab and could differentiate into many[19] human cell types.[20] Unlike how researchers previously extracted hESC from human embryos, Yamanaka and his team did not derive the cell lines from non-implanted human embryos, but instead from adult cell lines (skin).[21] Within a month of the Yamanaka paper, a second group published a similar method for reprogramming adult cells into stem cells,[22] showcasing the appetite for stem cell research methods that didn't require hESCs. After the two initial papers, many scientists around the world reproduced the scientists' results, perfected methods to create iPSCs, and studied the differences between iPSCs and hESCs.

Today, researchers routinely use iPSCs for projects that previously would have required hESCs, but do not require human embryos.[23] But the benefits of

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17 *Id*. at 93-95 ("National Institute of Health (NIH) funding, the life's blood of American academic biomedical research, was not available for research trying to develop hESC lines . . . Federal financial support for hESC research became a key issue in political races in the early 2000s, with many Republican candidates adopting the pro-life movement's opposition to any research in which babies (embryos) were killed or harmed and many Democratic candidates arguing that this research was necessary to cure many diseases of living children and adults."); President George H.W. Bush, Address from the Bush Ranch on Stem Cell Research, (Aug. 9, 2001, 8:01 AM) (transcript available at https://perma.cc/T8RR-TB7J). The harsh political response to hESCs mirrors the type of outcry that I hope will not happen with stem-cell based embryo model research.

18 *See* Kazutoshi Takahashi et al., *Induction of Pluripotent Stem Cells from Adult Human Fibroblasts by Defined Factors*, 131 CELL 861 (2007). The Yamanaka group announced the creation of mouse iPSCs one year earlier, *see* Kazutoshi Takahashi & Shinya Yamanaka, *Induction of Pluripotent Stem Cells from Mouse Embryonic and Adult Fibroblast Cultures by Defined Factors*, 126 CELL 663 (2006). Yamanaka's discovery of the necessary cell factors to induce iPSCs in both animals won him the 2012 Nobel Prize in Physiology or Medicine. *See* Press Release, *Nobel Prize, The Nobel Prize in Physiology or Medicine (2012),* https://perma.cc/JBX9-8L87.

19 While it would be wonderful to know exactly how many human cell types iPSCs can be differentiated into, this is a tricky question. The scientific community is currently debating how to define a "cell type" and new protocols are still being published with new cell "type" differentiations. People often estimate human bodies contain about 2,010 cell types, but defining cell types and cell states with new technology complicated the question. *See* Cole Trapnell, *Defining Cell Types and States with Single-Cell Genomics*, 25 GENOME RSCH. 1491 (2015).

20 *See* Takahashi et al., *supra* note 18.

21 *See id*. at 869 ("HDF from facial dermis of 36-year-old Caucasian female and HFLS from synovial tissue of 69-year-old Caucasian male were purchased from Cell Applications, Inc.").

22 *See* Junying Yu et al., *Induced Pluripotent Stem Cell Lines Derived from Human Somatic Cells*, 318 SCIENCE 917 (2007).

23 *See* Jimmy E. Hokatem et al., *Blood Derived Induced Pluripotent Stem Cells (iPSCs): Benefits, Challenges and the Road Ahead*, 6 J. ALZHEIMERS DISEASE & PARKINSONISM (2016).

iPSCs for research extend beyond developmental and regeneration studies previously performed with hESCs. For example, iPSCs can be used to better understand the molecular bases for genetic diseases.[24] Researchers generate iPSCs from living adults and test how genetic variants may contribute to a patient's specific disorder in different cell types.[25] By treating iPSC-derived cells with biological or chemical agents, researchers can test potential therapeutics at a cellular level.[26] Researchers also aim to regenerate tissue for transplants from individual patients directly to avoid the immune system avoidance effects that currently complicate tissue transplant recovery.[27]

C. Stem Cell-based Embryo Models Expand the Potential For How iPSCs Can Be Used to Research Human Biology

Researchers and physicians want to understand embryonic development to better understand human biology, as well as diseases that result from disruption of developmental processes.[28] Because iPSCs have the capacity to differentiate into all cells in the human body, they present an optimal system for studying embryonic structures and processes. Stem cell-based embryo model research began when researchers started generating unorganized balls of cells from iPSCs.[29] In an effort to better mimic human embryo development in the uterus, researchers then discovered ways to control cellular patterning to create organized embryo models.

Stem cell-based embryo models can be grouped by their level of organization and complexity, as unorganized, non-integrated, and integrated models.[30]

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24 *See* Amanda E. Yamasaki et al., *Understanding the Genetics Behind Complex Human Disease with Large-scale iPSC Collections*, 18 GENOME BIOLOGY (2017).

25 *See, e.g.*, Jenne Tran et al., *Genetic Predispositions of Parkinson's Disease Revealed in Patient-Derived Brain Cells,* 6 NPJ PARKINSON'S DISEASE (2020).

26 *See, e.g.*, Ruthellen H. Anderson & Kevin R. Francis, *Modeling Rare Diseases with Induced Pluripotent Stem Cell Technology*, 40 MOLECULAR & CELLULAR PROBES 52 (2018).

27 *See* Vimal K. Singh et al., *Induced Pluripotent Stem Cells: Applications in Regenerative Medicine, Disease Modeling and Drug Discovery*, 3 FRONTIERS IN CELL & DEVELOPMENTAL BIOLOGY 1, 4-12 (2015) (providing more explanation and examples of potential iPSC research).

28 Fu et al., *supra* note 4, at 134.

29 Rhodes et al., *supra* note 10 ("[Embryoid bodies] are three dimensional aggregates of spontaneously and asynchronously differentiating cells; that is, they contain developmentally diverse cell types from all three germ layers. EB formation has been used to verify stem cell pluripotency for decades."). "Embryoid bodies" is a term used to describe unorganized stem cell-based embryo bodies. I have decided not to use this term for consistency and to follow guidelines proposed by Clark et al. Clark et al, *supra* note 3, at 1418-19 ("In addition, to best reflect the state and the envisioned applications of these structures made from stem cells, the use of the umbrella term 'embryo model' or 'stem cell based embryo model' is encouraged, while the use of the term 'synthetic embryo' or 'artificial embryo' or 'embryoids' should be avoided.").

30 The International Society for Stem Cell Research (ISSCR) released a report in May

Unorganized models, sometimes termed embryoid bodies, model early development, because individual cells follow development trajectories closely resembling how cells develop in the human body.[31] The individual cells in these models have no potential to self-organize into the necessary structures for human life, but the cells representing each of the three developmental trajectories appear after 8 days in a dish.[32] Non-integrated stem cell-based models represent a more complex model for human development research. Non-integrated models contain cells organized into embryo-like structures, but they do not contain the full spectrum of cell types necessary for in vivo development.[33] Non-integrated models may model specific stages of early development, such as gastrulation,[34] without passing through each of the preceding developmental stages, such as the initial embryonic cell divisions.[35]

Integrated stem cell-based embryo models are the most complex models because they contain the relevant embryonic and extra-embryonic structure and could potentially develop further under the right conditions.[36] More specifically, integrated cellular models contain cells mimicking the cells that become the embryo and those that support life in the womb, such as trophoblasts.[37] While researchers have not implanted these models into a womb, they have proposed putting these models on a layer of human endometrial cells as a next step for developmental researchers to explore.[38]

2021, outlining (among other concepts) a categorical system for defining stem cell-based embryo models. Clark et al., *supra* note 3, at 1417-18.

31 *Id*. at 1417.

32 See Rhodes et al., *supra* note 10. The three developmental trajectories for human cells are the three germ layers: endoderm, ectoderm, and mesoderm. All human cells come from one of these three categories. *See* Kate MacCord, *Germ Layers, Embryo Project Encyclopedia* (Sept. 17, 2013), https://perma.cc/UBC6-M254.

33 Non-integrated stem cell-based embryo models: These stem cell-based embryo models will experimentally recapitulate some, but not all aspects of the peri-implantation embryo, for example differentiation of the embryonic sac or embryonic disc in the absence of extraembryonic cells. These stem cell-based embryo models do not have any reasonable expectations of specifying additional cell types that would result in formation of an integrated embryo model. Gastruloids are an example of a non-integrated stem cell-based embryo model
The International Society of Stem Cell Research, *ISSCR Guidelines for Stem Cell Research and Clinical Translation*, Version 1.0, 9, 64 (May 2021), https://perma.cc/Z5K2-RKT7

34 *See* Fu et al., *supra* note 4, at 133 (Box 1) ("Gastrulation describes the process by which the three definitive germ layers of the embryonic compartment of the conceptus are formed. Gastrulation begins around day 14 in humans.").

35 Clark et al., *supra* note 3, at 1419.

36 *See* The International Society of Stem Cell Research, *supra* note 33, at 64.

37 *See* Yu et al., *supra* note 2, at 621.

38 *See id*. at 624 fig. 4f ("Schematic summary of human blastoid formation from naive human PSCs and their potential applications.").

D. Human Subject Research Ethical Standards Provide a Framework for the Regulations Protecting Research Participants

The progress toward creating organized embryo models described above demonstrates how scientists are getting closer to creating functional, implantable human embryos from iPSCs. To prepare for that possibility, lawyers and policymakers need to evaluate the ability of current regulations to prevent unsafe or unethical research, such as research that takes away participant autonomy.[39] The following sections will explain the regulatory and legal safeguards designed to protect human subject research participants and how they apply in stem cell-based embryo model research.

E. Informed Consent Protects Participant Autonomy

To ensure safe and ethical research practices, the Code of Federal Regulations outlines rules and procedures for most human subject research in a set of regulations referred to as the Common Rule.[40] A researcher must follow specific procedures when he or she "(i) Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or (ii) Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens."[41] Under these procedures, researchers must obtain approval for research plans from an Institutional Review Board (IRB).[42] A key component of the IRB approval process evaluates the availability and thoroughness of the researchers' informed consent plans.

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39 *See, e.g.*, The International Society of Stem Cell Research, *supra* note 33 (developing guidelines proposed to address cultural, political, legal, and ethical issues with stem cell research); Aach et al., *supra* note 7 (calling for regulatory changes beyond removal of the fourteen-day rule to address ethical issues with synthetic embryo model research); Nicolas et al., *supra* note 3 (recommending the development of consistent and clear regulations to address ethical issues emerging with the development of stem cell-based embryo models).

40 The National Institute of Health implemented the Common Rule with 3 provisions. *See* Protection of Human Subjects, 45 C.F.R. § 46 (2018). The burden-reducing provisions include (1) the 2018 Requirements' definition of "research," which deems certain activities not to be research, (2) removal of the requirement for annual reviews for certain categories of research, and (3) removal of the requirement for Institutional Review Boards (IRBs) to review grant applications related to the research. *See* NAT'L INST. HEALTH, NOT-OD-19-050, NIH IMPLEMENTATION FINAL RULE ON FED. POL'Y. PROT. HUMAN SUBJECTS (COMMON RULE) (2019), https://perma.cc/XC62-D225.

41 Protection of Human Subjects, 45 C.F.R. § 46.102(e)(1) (2018).

42 *Id.* § 46.109. IRBs review research plans to ensure they uphold the ethical principles outlined in the Belmont Report and codified in the federal regulations. *See id.; see also* Belmont Report, *supra* note 5. They evaluate how researchers plan to uphold ethical principles of respect for persons, beneficence, and justice. Researchers must show they will minimize risks to participants, provide a reasonable relationship between risks and benefits, select subjects in an equitable way, and protect subject privacy. Protection of Human Subjects, 45 C.F.R. § 46.109 (2018)*; see also* Belmont Report, *supra* note 5.

Informed consent practices ensure researchers demonstrate "respect for persons," meaning "individuals [are] treated as autonomous agents" and "persons with diminished autonomy are entitled to protection."[43] Informed consent creates a contractual relationship between the researchers and subject, signifying that the subject has received information on the study, comprehends its risks and benefits, and voluntarily enters the study.[44]

Cells or tissue taken directly from the body (primary cells) can be manipulated in the laboratory and used for research only for a finite amount of time.[45] By established scientific protocols, researchers can transform primary cells into cell lines that have the ability to live and reproduce indefinitely.[46] Transformed cell lines, including iPSCs, enable scientists to perform multiple studies without recollecting new material, and to integrate data from multiple experiments to answer novel research questions.[47]

For new research with previously collected and lab-maintained cell lines, IRBs do not require new informed consent.[48] Rather, at the time of collection, participants typically grant "broad consent" for storage, maintenance, and secondary research use of their materials.[49] The standard for describing how samples will be used in the future is lower than true informed consent procedures that are approved by IRBs.[50] At collection, researchers must only provide participants with "sufficient information such that a reasonable person would expect that the

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43 Belmont Report, *supra* note 5.

44 *See* Valerie Gutmann Koch, *A Private Right of Action for Informed Consent in Research*, 45 SETON HALL L. REV. 173, 192 (2015) (discussing *Grimes v. Kennedy Krieger Inst., Inc*., 782 A.2d 807 (Md. 2001)); Protection of Human Subjects, 45 C.F.R. § 46.116 (2018) (outlining the elements of informed consent including information presented to subject).

45 *Primary Cell Culture Basics*, MILLIPORE SIGMA, https://perma.cc/4BJ3-6ZJY.

46 *Id.*

47 *See, e.g.,* Leah Samuel, *5 Important Ways Henrietta Lacks Changed Medical Science*, STAT (April 14, 2017), https://perma.cc/PKK2-HNQM (highlighting medical advances made possible by immortal cell line derived from Henrietta Lacks' cancer cells); Ian Streeter et al., *The Human-induced Pluripotent Stem Cell Initiative – Data Resources for Cellular Genetics*, 45 NUCLEIC ACIDS RSCH. D1, D691 (Oct. 12, 2016) (announcing over 500 iPSC lines available for reuse in additional studies); Bryan J. Pavlovic et al., *A Comparative Assessment of Human and Chimpanzee iPSC-derived Cardiomyocytes with Primary Heart Tissues*, 8 SCIENTIFIC REPS. (2018) (demonstrating value of iPSC-derived tissues to study primate tissues that are no longer available for collection).

48 Protection of Human Subjects, 45 C.F.R. § 46.116(a) (2018).

49 *Id.* § 46.116(d).

50 *Compare* Protection of Human Subjects, 45 C.F.R. § 46.116(b)(1) (2018) ("A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures that are experimental") *with* Protection of Human Subjects, 45 C.F.R. § 46.116(d)(2) (2018) ("A general description of the types of research that may be conducted with the identifiable private information or identifiable biospecimens. This description must include sufficient information such that a reasonable person would expect that the broad consent would permit the types of research conducted.").

broad consent would permit the types of research conducted."[51] Stem cell-based embryo research teams often do not collect primary cells, so they do not interact with donors directly. Rather, they use cell lines generated from human tissues previously collected for other studies.[52] As a result, the researchers rely on previously approved IRB protocols and this so-called broad informed consent.[53] Broad informed consent remains the current standard of practice. Nonetheless, as will be described further below, broad informed consent is not adequate – legally or ethically – to protect research participant autonomy.

F. Embryo and Embryo Model Research Requires Additional Safeguards

Research communities and regulators can recommend additional safeguards beyond what is required by the Code of Federal Regulations when research has the potential to cross moral or ethical boundaries.[54] For example, when the possibility of culturing human embryos for research emerged around 1980, international ethics, governmental, and research communities adopted a fourteen-day rule.[55] The rule prevented researchers from growing embryos for research longer than fourteen days.[56] The rule sought to balance any ethical reservations associated with embryo research with the research's potential benefits. The fourteen-day rule remains relevant to stem cell-based embryo model research. In 2021, the largest stem cell professional society, the International Society for Stem Cell Research (ISSCR), outlined recommendations for safe stem cell-based embryo model research, which included a discussion on the fourteen-day rule.[57] The ISSCR guidelines provide recommendations agreed upon by stem cell experts,

51 *Id.*

52 *See, e.g.*, Rhodes et al. *supra* note 10; Yu et al., *supra* note 2; Zheng et al., *supra* note 10.

53 Email from Katherine Rhodes, Staff Scientist at University of Chicago, to author (Nov. 4, 2021, 12:15 PST) (on file with author) (relaying conversation between K. Rhodes and Y. Gilad); Email from H. Bertram, research manager for Heinz C. Prechter Bipolar research program at the University of Michigan, to author (Oct. 27, 2021, 9:40 PST) (on file with author) (sending the consent form from the study the cell lines were collected from); Email from Jun Wu, Associate Professor at UT Southwestern Medical Center, to author (Oct. 27, 2021, 8:07 PST) (on file with author) (describing cell line consent structure).

54 *See, e.g.*, Eric S. Lander et al., Comment*, Adopt a moratorium on heritable genome editing*, 567 NATURE 145, 165 (Mar. 14, 2019) (calling for global moratorium on heritable genome editing research).

55 *See* Kendall Powell, *What's Next for Lab-Grown Human Embryos?*, 597 NATURE 22, 23 (2021); Giulia Cavaliere, *A 14-Day Limit for Bioethics: The Debate Over Human Embryo Research*, 18 BMC MED. ETHICS 38 (May 30, 2017).

56 *See* UK Department of Health and Social Security, REP COMM. INQUIRY HUM. FERTILISATION & EMBRYOLOGY 89 (Her Majesty's Stationery Office, 1984); Ad Hoc Group of Consultants to the Advisory Committee to the Director, NIH. Report of the Human Embryo Research Panel 67 (US Government Printing Office, 1994); Aach et al., *supra* note 7, at 2.

57 *See* The International Society of Stem Cell Research, *supra* note 33, at 12.

doctors, ethicists, lawyers, and industry representatives.[58] The recommendations can then be adopted by public regulators to promulgate laws and regulations on a country-by-country basis.[59]

In addition to recommending an end to the traditional fourteen-day rule, the ISSCR report provides recommendations for when stem cell-based embryo model research demands additional institutional oversight beyond an IRB.[60] Under the ISSCR recommendation, unorganized models are exempt from additional oversight, non-integrated models may be subject to additional oversight pending local policy, and integrated models must always be subject to review by a specialized scientific and ethics review process.[61] On one hand, the committee recommends (1) inclusion of stem cell-specific experts during procurement of fresh human tissue or cells for stem cell research and (2) documented consent for research uses including development of iPSCs and embryos.[62] On the other hand, cell lines are compliant with ISSCR's guidelines under their original consent structures.[63] Thus, the recommendations acknowledge the need for reform but do not go far enough to adequately address problems created by current studies using previously collected cell lines for embryo model research.

This section has served as a primer to the scientific issues that underlie this Note, as well as the existing regulatory frameworks that apply to human subject and embryo research. Technological advances in stem cell research and stem cell-based embryo research have expanded the amount of time cells can be kept in laboratories and the ways the cells can be manipulated or transformed into new cell types. Traditional human subject research guidelines, as well as community specific guidelines, such as those proposed by the ISSCR, serve as both an ethical and legal framework to help ensure researchers protect participant dignity and welfare. In the following sections, I will outline why the novelties of stem cell-based embryo research call for novel consent approaches for research participation, beyond what has been proposed by the ISSCR.

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58 *Id.* at 3.

59 Megan Munsie, *Setting the Standards – New Stem Cell Research Guidelines Released*, ISSCR (Aug. 5, 2021), https://perma.cc/QRL9-VU2S.

60 The International Society of Stem Cell Research, *supra* note 33, at 9 (describing categories for stem cell-based embryo models and when additional oversight is necessary).

61 *See id.;* Clark et al., *supra* note 3, at 1417.

62 The International Society of Stem Cell Research, *supra* note 33, at 15 (ISSCR 2.3.1 and 2.3.2).

63 *Id.* at 15 (ISSCR 2.3.1 and 2.3.2) (ISSCR 2.3); *but cf. id*. at 16 (ISSCR 2.3.1 and 2.3.2) (describing reconsent only for reproductive purposes under ISSCR 2.3.2).

II. Stem Cell-based Embryo Models Create Potential for Ethical and Legal Concerns

A. Current Consent Practices Take Autonomy from Research Participants

Advances in stem cell-based research require that we reevaluate the suitability of traditional safeguards to protect today's research participants. By creating stem cell-based embryo models, scientists have pushed the traditional boundaries of what we have thought possible with laboratory-based cell culture systems.[64] The new methods allow the creation of embryo models with the potential for life, yet only general consent has been obtained for the underlying material. Specifically, at the time of cell collection and original donor consent, the researchers were only required to provide "sufficient information such that a reasonable person would expect that the broad consent would permit the types of research conducted."[65] Scientists are breaching this standard – thus taking away autonomy from research participants – because stem cell-based embryo model research does not fall into the category of research a person would expect when they provide general consent or the consent is taken prematurely for the experiment. The following case studies further explore this breach.

1. Case study 1: *Rhodes et al.* – unorganized model, change of subject matter

Rhodes et al. generated unorganized embryo models from banked iPSC lines maintained in their research lab.[66] In 2018, Banovich et al. published the reprogramming of iPSC lines from lymphoblastoid cell lines (LCLs) that they ordered from Coriell Institute for Medical Research, a not-for-profit research organization.[67] LCLs are immortal B cells originally isolated from blood. They are cell

64 *Compare* Charis-P. Segeritz & Ludovic Vallier, *Cell Culture Growing Cells as Models Systems In Vitro*, in BASIC SCIENCE METHODS FOR CLINICAL RESEARCHERS 151-172 (Morteza Jalali, Francesca Yvonne Louise Saldanha & Mehdi Jalali eds., 2017) (explaining the setup, maintenance, and usage of cell culture laboratories), *with* Joni H. Ylostalo, *3D Stem Cell Culture*, 9 CELLS 10 (2020) (highlighting 3D culturing of stem cells as an advanced research method).

65 Protection of Human Subjects, 45 C.F.R. § 46.116(d)(2) (2018).

66 Rhodes et al., *supra* note 10. After allowing the models to develop for 21 days, Rhodes et al. collected data on the genes expressed at a single cell level. By comparing these data to known cell type markers and published data from human fetal tissues, the research team assigned each of the cells in their model to a human embryonic cell type. At just 21 days, Rhodes et al. identified primitive streak and neural crest cells. Using computational methods, the authors traced developmental trajectories to show that cells in the model differentiated similarly to how they would during in vivo gastrulation.

67 *See* Nicholas E. Banovich et al., *Impact of regulatory variation across human iPSCs and differentiated cells*, 117 GENOME RSCH. 122 (2018), https://perma.cc/3KX3-SLBF; email from Jonathan Burnett, Stem Cell Lab Manager at University of Chicago, to author

lines commonly used in research, because they are easy to create from blood samples and easy to maintain in the lab.[68] Coriell had maintained and distributed the LCLs since the International HapMap Consortium collected the original samples.[69] In both Banovich et al. and Rhodes et al., the researchers were not required to collect additional consent from cell donors or apply for approval from an IRB. Rather, the lead researcher in both studies, Dr. Yoav Gilad, communicated to Coriell his intent to use the LCLs for iPSC research and proceeded with the work.[70] Thus, the current stem cell-based embryo research falls under the original broad consent obtained by the HapMap Project.[71]

In the early 2000s, the International HapMap Consortium collected blood samples from individuals from four populations to study patterns of genetic variation across the world.[72] Researchers from outside the original project, including Rhodes et al. and Banovich et al., have now used the cell lines for a wide range of research projects.[73] At the time of collection, the HapMap Consortium researchers foresaw several ethical and social issues with their wide-reaching genomics project.[74] As a result, the consortium included bioethicists as well as social and behavioral scientists.[75] The writings of these consortium members provide insight into the types of research to which participants understood they had consented, such as research into the relationship between genetic variation

(Nov. 29, 2023, 8:19 PST) ("As an author on the paper, I can confirm that the cell lines were originally ordered from Coriell.").

68 *See* Jae-Pil Jeon, *Human Lymphoblastoid Cell Lines in Pharmacogenomics*, in Handbook of Pharmacogenomics and Stratified Medicine 89, 90 (2014); https://perma.cc/L3BB-VZUU. *See Lymphoblast Culture FAQ*, CORIELL INST. MED. RSCH., https://perma.cc/E5C8-CTJG.

69 Charles Rotimi et al., *Community Engagement and Informed Consent in the International HapMap Project*, 10 CMTY. GENETICS 186, 187 (2007).

70 Email from Katherine Rhodes, Staff Scientist at University of Chicago, to author (Nov. 4, 2021, 12:15 PST) (on file with author) (relaying conversation between K. Rhodes and Y. Gilad).

71 *See HapMap Project*, CORIELL INST. MED. RSCH., https://perma.cc/TT9M-SK6V ("Donors gave broad consent to future uses of the samples, including their use for extensive genotyping and sequencing, gene expression and proteomics studies, and all other types of genetic variation research, with the data publicly released.").

72 The four populations include the Yoruba from Ibadan, Nigeria, Japanese from Tokyo, Japan, Han Chinese from Beijing, China and CEPH (a population of US residents with northern and western European ancestry). Rotimi et al., *supra* note 69, at 188-89.

73 *See, e.g.*, Banovich et al., *supra* note 67; Rhodes et al., *supra* note 10; Andrew G. Clark et al., *Ascertainment Bias in Studies of Human Genome-wide Polymorphism*, 15 GENOME RSCH. 122 (2005); David B. Goldstein & Gianpiero L. Cavalleri, *Genomics: Understanding Human Diversity*, 437 NATURE 1241 (2005); Yang I. Li et al., *RNA Splicing is a Primary Link between Genetic Variation and Disease*, 352 SCIENCE 600 (2016).

74 *See* International HapMap Consortium, *Integrating Ethics and Science in the International HapMap Project*, 5 NATURE REVS. GENETICS 467 (2004) (outlining ethical considerations such as privacy and community engagement and presenting the consortium groups developed to consider the ethical issues at the project's conception).

75 Rotimi et al., *supra* note 69.

and health.[76]

Given the consent process, a reasonable person in the position of the cell donors for the HapMap project, whose cells were used in the Rhodes et al. project, likely did not receive sufficient information to expect use of their cells in stem cell-based embryo research. Rhodes et al. specifically used the cell lines derived from the samples collected from Yoruba individuals living in Ibadan, Nigeria.[77] The original research project focused on answering questions about genetic variation, not about cellular or developmental biology.[78] The consent documents disclosed that the cells and resulting data would be used for "studies of the biology of DNA, how new variations arise, the genetic history of human groups, and how people from different parts of the world are related."[79] Given this expected use, the research team discussed potential concerns with the research participants, such as group stigmatization and discrimination.[80] While we do not know if the potential for stem cell research would have influenced participants' decisions to consent, several Yoruba individuals expressed concerns about disposal plans for unused blood samples and the possibility of human cloning.[81] Through these concerns, we can infer that the community felt a pseudo-moral connection to the biological material and did not want it to be transformed for other purposes, such as cloning or the next hot topic in biological research.

The HapMap researchers added additional safeguards to protect participant autonomy in ways that are not required by the broad consent. The researchers created a Community Advisory group (CAG) to serve as a liaison between the Yoruba community and Coriell.[82] The CAG would not and has not communicated with individual donors regarding their cells, but the community could request withdrawal of all of their cells from future research.[83] In theory, this structure helps to uphold ethical principles despite general consent for future research.

In practice, it is unclear whether the CAG maintains a relationship with the Yoruba individuals or continues to protect participant autonomy. First, since

76 International HapMap Consortium, *supra* note 74; Rotimi et al., *supra* note 69, at 187, 193.

77 Rhodes et al., *supra* note 10, at 16.

78 *See id.* at 1-3.

79 Rotimi et al., *supra* note 69, at 192.

80 *See id.*

81 Individuals with no background in biomedical research worried about blood handling. The consent forms "forbade their use for reproductive cloning. The reference to cloning was included because of concerns expressed in some communities about this possibility." *Id.*

82 *Id.* at 189.

83 *Information for Investigators*, CORIELL INST. MED. RSCH., https://perma.cc/5WAP-DXCU.

2007, Coriell has not published and distributed HapMap newsletters about current research and findings.[84] Second, although Coriell advises researchers to notify them with any publications resulting from the use of the samples, the recommendation is unlikely to be followed.[85] Finally, although Coriell prohibits secondary distribution of cell lines, research groups actively share Yoruba iPSCs.[86] In the Rhodes et al. scenario the issue is two pronged: (1) the safeguards to preserve donor autonomy have decayed since project initiation, and (2) the current safeguards remain insufficient to protect donors.

2. Case study 2: *Yu et al.* – integrated model, change in subject matter and premature consent

Yu et al. cultured 20-30 iPSCs in a three-dimensional matrix to develop integrated stem-cell based embryo models, the most complex of the three types.[87] According to the researchers, the models closely mimic the group of human fertilized cells seen at embryonic development days 6 to 8.[88] Yu et al. created integrated stem cell-based embryo models using iPSCs originally reprogrammed from the cells of connective tissue, fibroblasts, collected from male neonate foreskin and ordered from a private, non-profit organization called American Type

84 *HapMap Community Newsletters*, CORIELL INST. MED. RSCH., https://perma.cc/NME9-ZZDF.

85 *Information for Investigators*, *supra* note 83 ("Investigators who use these samples are asked to be sensitive to the possible implications of their research for the sample donors and their communities and populations. Investigators should describe their study results with care and attention to the potential broader implications of their research. Investigators should adhere to the Guidelines for Referring to Populations in Publications and Presentations."). I published a paper with Yoruba LCLs in 2020 under the supervision of well-established and respected researchers. My team never discussed sending our publication to Coriell and I had never heard of this policy until I began research for this paper. On January 25, 2022, I sent an email to the Coriell contact on the site asking for a list of publications that teams had reported to them. As of this writing, April 29, 2024, I have not received a response.

86 *Compare Secondary Distribution and Shared Use of Cell Cultures and DNA Samples from the NHGRI Collection,* CORIELL INST. MED. RSCH., https://perma.cc/742Z-RPSA, *and* Email from Jonathan Burnett, Stem Cell Lab Manager at University of Chicago, to author (Nov. 16, 2021, 8:56 PST) (on file with author) ("The Gilad lab shares Yoruba[] (YRI) iPSC lines with labs across the globe with no restrictions or limitations for the benefit of the scientific community. The lines we shared are an important and unique resource for many genetic studies that could not be obtained from any other source.").

87 Yu et al., *supra* note 2. The protocol included sequentially treating the cells with particular molecules that serve as developmental factors; the authors created an integrated stem cell-based model to study pre-implantation human blastocysts.

88 *Id.* at 621-24 (explaining that similarities to blastocysts include structurally flattening, GATA6+ and GATA3+ cells surround SOX2+ cells, and dimensions similar to in vivo embryo day 6 (e6), the models also contain an inner region of epiblast and hypoblast like cells outlined by trophoblast cells.).

Culture Collection (ATCC).[89] The ATCC manages a biological repository from which researchers can order high quality, authenticated cell lines and other biological materials for a wide range of research projects.[90] According to the lead author for the Yu et al. publication, Dr. Jun Wu, the researchers did not need to communicate the intent to reprogram the fibroblasts into iPSCs to the organization maintaining the cell lines, because the Material Transfer Agreement (MTA) did not require such notice.[91] Further, because the cells came deidentified, the researchers did not need to reapply for IRB approval for this work.[92] The ATCC does not provide information about when or where the samples were collected. The detailed description for one of the lines identifies the donor as a Caucasian male neonate.[93] The ethnicity of the second line is not published, but the site does report that they received the line in April 2000.[94]

Practically, generating fibroblast cell lines from neonate foreskin is preferred to collecting skin from adults. Collecting adult skin requires a 3.5mm – 4.0mm skin punch biopsy. The procedure comes with risks such as the risk of infection, adverse reactions to anesthetics, and scarring.[95] In comparison, doctors remove foreskin during routine circumcisions and, if not donated, the material would become medical waste. Ethically, however, foreskin donation presents challenges because parents must provide consent for their child that goes beyond the ordinary consent for the medical procedure. [96] In principle, parental consent can stand in for donor consent in situations where the donated material will be anonymized, because the effects of the donation will never be known to the child when they

89 *See* Yu et al., *supra* note 2; Jun Wu et al., *An Alternative Pluripotent State Confers Interspecies Chimaeric Competency*, 521 NATURE 316 (2015); Jun Wu et al., *Interspecies Chimerism with Mammalian Pluripotent Stem Cells*, 168 CELLS 473 (2017).

90 *About Us*, AM. TYPE CULTURE COLLECTION, https://perma.cc/HG6S-C9PU.

91 *Material Transfer Agreement*, AM. TYPE CULTURE COLLECTION, https://perma.cc/ER79-2EY8; Email from Jun Wu, Associate Professor at UT Southwestern Medical Center, to author (Oct. 27, 2021, 8:07 PST) (on file with author) (describing how authors ordered cell lines from ATCC).

92 Email from Jun Wu, Associate Professor at UT Southwestern Medical Center, to author (Oct. 27, 2021, 8:07 PST) (on file with author) (describing how authors ordered cell lines from ATCC).

93 *CCD-1112Sk CRL-2429*, AM. TYPE CULTURE COLLECTION, https://perma.cc/4HGG-HYKG.

94 *BJ CRL-2522*, AM. TYPE CULTURE COLLECTION, https://perma.cc/W9MQ-FV47.

95 Stefanie Raab et al., *A Comparative View on Human Somatic Cell Sources for iPSC Generation*, 2014 STEM CELL INT'L (2014).

96 *See* Molly Glick, *Why Human Foreskin Is a Hot Commodity in Science,* DISCOVER (Jul. 26, 2021, 10:00 AM), https://perma.cc/3L5R-2LYF; *see, e.g.*, Nilendran Prathalingam et al., *Production and Validation of a Good Manufacturing Practice Grade Human Fibroblast Line for Supporting Human Embryonic Stem Cell Derivation and Culture*, 3 STEM CELL RSCH. THERAPY (2012); Naohisa Wada et al., *Human Foreskin Fibroblasts Exert Immunomodulatory Properties by a Different Mechanism to Bone Marrow Stromal/Stem Cells*, 20 STEM CELLS & DEV. 647 (2010) (reporting parental informed consent for neonatal fibroblast donation).

reach consenting age. However, technological advances in computing and genetics now make it possible to reidentify donors.[97] To some, reidentification after the child becomes an adult compels researchers to obtain reconsent when the donor reaches maturity.[98] As a result, a reasonable person in the parents' position may have been deterred from making the decision to donate foreskin if they thought there was a chance that child would not have wanted to participate in the research as an adult.

We do not have information about the original donor or donor community. Thus, we cannot inquire into the position of the donor's parents about iPSC or integrated stem cell-based embryo generation. Even if we could recontact the parents or use DNA matching to find the original donors, recontact may—as I will detail below—introduce unnecessary stress for individuals unaware of the donation.

3. Case study 3: *Zheng et al.* – nonintegrated model, change of subject matter

Zheng et al. generated a non-integrated embryo model to study post-implantation development in the lab.[99] The model resembled a human embryo directly before the onset of gastrulation.[100] Unlike in the previous two examples, the research participants in Zheng et al. consented to the researchers using their cells

97 *See* Melissa Gymrek et al., *Identifying Personal Genomes by Surname Inference*, 339 SCIENCE 321 (2013) (establishing that samples can be reidentified even without access to a reference genome). There are also privacy risks of reidentification. These are beyond the scope of this Note.

98 *See* Blake Murdoch et al., *Reconsenting Pediatric Research Participants for Use of Identifying Data,* 49 J. MED. ETHICS 106, 106 (2023) (identifying the emerging concerns of reidentification of anonymized data as a reason to seek reconsent).

99 *See* Zheng et al., *supra* note 10, at 421. The protocol included group inducing organization by using a device with small chambers and channels to control rate and volume and the researchers combined the cells with known biological triggers of early development, such as, BMP4.

100 The researchers identified primitive streak development and primordial germ cell-like cells. Primordial germ cells are precursors to egg and sperm. Germ line cells are important for reproduction because they pass genetic material to the next generation.

> Here we report that human pluripotent stem cells (hPSCs) in a microfluidic device recapitulate, in a highly controllable and scalable fashion, landmarks of the development of the epiblast and amniotic ectoderm parts of the conceptus, including lumenogenesis of the epiblast and the resultant pro-amniotic cavity, formation of a bipolar embryonic sac, and specification of primordial germ cells and primitive streak cells.

Id. at 422.

to generate iPSCs.[101] Zheng et al. used a human iPSC line collected and maintained by the University of Michigan Stem Cell Core.[102] Researchers at the University of Michigan originally created the iPSCs from skin cells collected for a bipolar disorder study.[103] The consent document describes iPSCs as cells with the capability to develop into any tissue type and the potential to survive indefinitely.[104] The study information section of the informed consent document further explains: "[t]his research will focus on the study of brain and nerve cells derived from the skin cells of people with a mental health condition in comparison with healthy controls. It is also possible that your cells could be used to study other diseases."[105]

Based on this information, it is not certain the participants or a reasonable person would have expected future researchers to create organized embryo models with their cells. Another section of the consent form outlines the potential for currently unknown uses of the cells:

> Other currently unknown uses. Science is always evolving and it is therefore difficult to determine exactly how these cells will be used in the future. *The University of Michigan will not permit your cells (including DNA or genes) to be used for reproductive research* or human "cloning". It is possible that your cells could be used to create a tissue-specific stem cell line, which could be transplanted into another human for the purpose of treating mental health or other disorders.[106]

While the stem cell embryo models have not been transplanted into a womb, a reasonable person may believe that the research in Zheng et al. is "reproductive research" because the researchers model early human development.[107] If so, the scientists did not merely take away autonomy from the research participant—they also breached informed consent.

Through changes in research subject matter and/or the time between cell collection and experiment, the examples above demonstrate that research participants did not have "sufficient information such that a reasonable person would

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101 Email from H. Bertram, research manager for Heinz C. Prechter Bipolar research program at the University of Michigan, to author (Oct. 27, 2021, 9:40 PST) (on file with author) (sending the consent form from the study the cell lines were collected for study. Informed consent document for study ID HUM00043228).

102 Zheng et al., *supra* note 10, at 426.

103 H. M. Chen et al., *Transcripts Involved in Calcium Signaling and Telencephalic Neuronal Fate are Altered in Induced Pluripotent Stem Cells from Bipolar Disorder Patients,* 4 TRANSLATIONAL PSYCHIATRY 1, 2 (Mar. 25, 2014).

104 Informed consent document, *supra* note 101, at 1.

105 *Id.*

106 *Id.* at 4 (emphasis added).

107 *See* Harvey L. Fiser & Paula K. Garrett, *Life Begins at Ejaculation: Legislating Sperm as the Potential to Create Life and the Effects on Contracts for Artificial Insemination*, 21 J. GENDER, SOC. POL'Y. & L. 39 (2012) (explaining that even current legislation misrepresents reproduction by, for example, failing to differentiate sperm, embryos, preimplantation embryos, and zygotes).

expect that the broad consent would permit the types of research conducted."[108] First, consent was collected too early for the current research studies. The consent agreements above took place before the current research became scientifically possible. Parents consenting on the behalf of their neonates also invokes a timing issue. Second, consent covered a distinct subject matter. The Yoruba population donated samples to help increase genetic diversity in genomic projects and the donors in Zheng et al. donated to advance mental health research. The samples have now been employed to understand embryology using a novel and controversial method. When researchers conduct experiments outside the scope of the original consent—with respect to when consent should be obtained or for which subject matter—the researchers violate the standard for consent on secondary research.

B. The Possibility of Legal Disputes Stifles Science and Challenges Legal Classification of Embryos

Current consent practices for stem cell-based embryo model research deprive research participants of autonomy by failing to provide sufficient information at the time of consent. The violation is particularly problematic in embryo model research, because Americans have wide ranging opinions on the definition of life and the morality of embryo research.[109] In the year prior to President Obama's removal of the restrictions on embryonic stem cell research, a study of 1,003 American adults assessed the division of opinions on the topic.[110] When asked if they agreed that "[a]n embryo is a developing human life, therefore it should not be destroyed for scientific or research purposes," 62% of the respondents agreed, with 48% strongly agreeing.[111] Respondents also disagreed as to whether embryos created for in vitro fertilization (IVF) should be used for research.[112]

If research participants fall into the group that strongly disagrees with embryo research, like other participants in similar circumstances, they may be inclined to pursue legal action for breach of informed consent.[113] The question of

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108 45 C.F.R. § 46.116(d)(2) (2018).

109 *See* Yuval Levin, *Public Opinion and the Embryo Debates*, 20 NEW ATLANTIS 47 (2008).

110 *See* Exec. Order No. 13,505, 3 C.F.R 229, 229 (Mar. 9, 2009); Levin, *supra* note 109, at 48.

111 Levin, *supra* note 109, at 52.

112 *Id.* at 53 (47% supported and 48% opposed the statement "Sometimes human embryos are created through in vitro fertilization with the intention of implanting them in a mother's womb to develop and be born, but for one reason or another, they are never used that way. In that instance, do you support or oppose using and therefore destroying those unwanted embryos for scientific research purposes?").

113 *See, e.g.*, Greenberg v. Miami Children's Hosp. Rsch. Inst., Inc., 264 F. Supp. 2d 1064 (S.D. Fla. 2003); Havasupai Tribe v. Ariz. Bd. of Regents, 220 Ariz. 214 (Ariz. Ct. App. 2008).

whether cell and tissue donors could bring a claim for breach of informed consent is not simple. In medical practice, patients can bring legal claims against their doctors for breach of informed consent.[114] When researchers stand in a doctor/patient relationship to a participant, the research participant may be able to bring a breach of informed consent lawsuit.[115]

Despite some scholars calling for a private right of action for research participants, healthy cell and tissue donors who participate in research do not yet have a private right of action.[116] In *Greenberg v. Miami*, the court ruled against plaintiff families who tried to use a breach of informed consent claim to recover from researchers who identified the genetic variant causing Canavan Disease.[117] The families donated money, medical information, and specimens to the researchers who then failed to make the resulting genetic tests "affordable and accessible" to Canavan families.[118] The court held that the researcher's relationship with the donors was not sufficient to justify a legal duty.[119]

Even without a successful claim for breach of informed consent, research participants have been able to recover from a research institution when they felt wronged. For example, in *Havasupai Tribe v. Arizona Board of Regents*, the Havasupai Tribe sued the Arizona Board of Regents and Arizona State University (ASU) claiming misuse of donated biological material.

The Havasupai settlement arose out of a consolidated case before the Court of Appeals of Arizona.[120] After a many-year relationship between the tribe and an anthropology professor at ASU, the tribe and the anthropology professor approached a genetics professor to study the high incidence of type two diabetes in the community.[121] Before collecting DNA samples from over 200 tribe members, the researchers educated the tribe about diabetes, blood sample testing, and genetic association testing.[122] The research participants signed an informed consent form that described the goal of the diabetes project and the potential secondary use of the samples for research on "behavioral/medical problems."[123]

After the researchers failed to identify a genetic link to diabetes in the tribe,

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114 *See* Gutmann Koch, *supra* note 44, at 176.

115 *Id.* at 196.

116 *See id.* at 202-10 (advocating for a private right of action for informed consent breach in research).

117 *Greenberg*, 264 F. Supp. 2d at 1066; Kayte Spector-Bagdady, *Governing Secondary Research Use of Health Data and Specimens: The Inequitable Distribution of Regulatory Burden between Federally Funded and Industry Research*, 8 J. L. & BIOSCIENCES 1, 10 (2021).

118 Spector-Bagdady, *supra* note 117, at 10.

119 *Greenberg*, 264 F. Supp. 2d at 1073; Spector-Bagdady, *supra* note 117, at 10.

120 Havasupai Tribe v. Ariz. Bd. of Regents, 220 Ariz. 214, 217 (Ariz. Ct. App. 2008).

121 *Id.* at 217-18.

122 *Id.*

123 Nanibaa' A. Garrison, *Genomic Justice for Native Americans: Impact of the Havasupai Case on Genetics Research*, 38 SCI., TECH'Y & HUMAN VALUES 201, 203 (2012).

the researchers concluded the diabetes project. Soon after, scientists at ASU requested and gained IRB approval for secondary research with the Havasupai DNA samples.[124] Without reconnecting with the tribe members, researchers studied schizophrenia and the population's migration patterns.[125] In 2003, a member of the Havasupai tribe learned about the additional work at a dissertation defense.[126] After following up with the graduate student researcher about the consent procedures and receiving, "a response that was equivocal at best," the tribal member approached the Havasupai Tribal council about mishandling of blood samples at ASU.[127]

The Havasupai case settled with the Havasupai Tribe receiving $700,000, funds for a tribal medical clinic, a school, and the return of tribe DNA samples.[128] The settlement means the case was never decided under a theory of breach of informed consent or property rights for the cells. However, the case "highlighted the effects of research harms on the community, challenged the appropriateness of certain types of research, and questioned the adequacy of informed consent."[129]

In addition to the direct negative impact on research participants in cases of breach of consent, these instances have several indirect impacts. First, they hurt those who could have benefited from the fruit of the research. The potential medical benefits of a successful collaboration between the Havasupai Tribe and Arizona State University will never be known. Second, an attempted, even if unsuccessful, lawsuit for breach of informed consent brings additional public harm. Through formal or even informal settlements, researchers would likely be forced to stop both the embryo model research and the other avenues of productive research currently conducted with the same iPSCs that had the potential health benefits.[130]

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124 *Id.*

125 The Havasupai would likely not have consented to this work. Schizophrenia is highly stigmatized in the Havasupai culture. Results from the evolutionary genetic studies to determine ancient human migratory patterns directly contradict the Havasupai belief that they originated directly from the Grand Canyon. *See* Garrison, supra note 123); *Havasupai Tribe*, 220 Ariz. at 218.

126 *Havasupai Tribe*, 220 Ariz. at 218.

127 *Id.*

128 See Garrison, supra note 123; Michelle M. Mello & Leslie E. Wolf, *The Havasupai Indian Tribe Case – Lessons for Research Involving Stored Biologic Samples*, 363 NEW ENGLAND J. MED. 204 (2010); Amy Harmon, *Indian Tribe Wins Fight to Limit Research of its DNA*, N.Y. TIMES (Apr. 21, 2010), https://perma.cc/Q6LW-VNMR.

129 Garrison, *supra* note 123, at 203; *see* LorrieAnn Santos, G*enetic Research in Native Communities*, 2 PROGRESS COMM. HEALTH P'SHIP 321 (2008).

130 iPSCs are used for a wide variety of productive research. iPSCs are used to better understand the molecular basis for genetic diseases. Researchers generate iPSC from living adults and test how genetic variants may contribute to the patient's specific disorder in different cell types. By treating iPSC-derived cells with biological or chemical agents, researchers can all treat the cells with different agents to test potential therapeutics at a cellular level. *See, e.g.*, Anderson & Francis, *supra* note 26. Researchers also aim to regenerate tissue for

Third, media coverage of breaches of consent leads the public to believe that such violations of participant privacy occur frequently, leading to further mistrust in science. For example, media covered the *Havasupai Tribe v. Arizona Board of Regents* case as a scandal and an attack on tribal autonomy.[131] Such media coverage might prevent the public from wanting to get involved with future research endeavors. The story of Henrietta Lacks and the HeLa cell line, made famous by Rebecca Skloot's provocative book, further demonstrate this point.[132] The lack of informed consent dominated the public discussion of the book and drove public concern about biospecimen research.[133] Even 10 years after the book's publication, research participants continued to ask about Henrietta Lacks when deciding whether to participate in research.[134] One participant noted that donating blood or tissues makes them feel vulnerable and, in their words, "I don't want to be Henrietta Lacks."[135] The mistrust in informed consent and the lack of interest in research participation resulting from media coverage of controversial studies have lasting negative impacts on scientific innovation.[136]

Without a formal way to recover for breach of informed consent, frustrated research participants may turn to property law to claw back ownership of their cells, thereby regaining control of their biological material.[137] While previously

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transplants from individual patients directly to avoid the immune system avoidance effects that currently complicate tissue transplant recovery. *See* Singh et al., *supra* note 27.

131 *See, e.g.*, Marija Potkonjak, *Havasupai Tribe files $50M lawsuit against ASU*, E. VALLEY TRIB. (Mar. 17, 2004), https://perma.cc/9VCU-LDHZ; Harmon, *supra* note 124; Paul Rubin, *Havasupai Tribe Win Nice Settlement from ASU in Scandalous Blood-Sample Case*, PHX. NEW TIMES (April 22, 2010), https://perma.cc/E45Q-UNLN.

132 REBECCA SKLOOT, THE IMMORTAL LIFE OF HENRIETTA LACKS (2010).

133 Matthew C. Nisbet & Declan Fahy, *Bioethics in Popular Science: Evaluating the Media Impact of The Immortal Life of Henrietta Lacks on the Biobank Debate*, 14 BMC MEDICAL ETHICS 1, 1 (2013) ("The informed consent theme dominated media discussion, with almost 39.2 percent of articles/transcripts featuring the theme as a major focus and 44.8 percent emphasizing the theme as a minor focus."); *see* Laura M. Beskow, *Lessons from HeLa Cells: The Ethics and Policy of Biospecimens*, 17 ANN. REV. GENOMICS HUM. GENETICS 395 (2016).

134 Sandra S.-J. Lee et al., *"I Don't Want to be Henrietta Lacks": Diverse Patient Perspectives on Donating Biospecimens for Precision Medicine Research*, 21 GENETIC MED. 107, 110 (2019).

135 *Id.*

136 This problem is exacerbated by the fact that the individuals who are the most mistrusting of researchers are also those underrepresented in biological and medical research studies. Thus, the consequences of mistrust extend beyond hurting what studies can be done; it also means that vulnerable communities are less likely to benefit from discoveries.

137 Regaining property rights to the material is also a strategy to recover on the financial gain that researchers and companies made using biological material. These arguments may come in the form of an unjust enrichment claim, like those made in an ongoing lawsuit by the Lacks family against Thermo Fisher Scientific Inc. *See, e.g.*, Craig LeMoult*, Thermo Fisher seeks dismissal of Henrietta Lacks' family's lawsuit regarding sale of her cells*, GBH NEWS (May 17, 2022), https://perma.cc/28RS-GR6B; Madeleine O'Neill, *Henrietta Lacks' Estate Will Amend Complaint, Delaying Decision in Lawsuit*, MD. DAILY REC. (Nov. 17, 2022), https://perma.cc/E3S6-RQN3.

unsuccessful,[138] new legal precedent suggests plaintiffs may have more luck arguing for a retained property right to embryo-like tissue. In 2022, the Supreme Court upheld a 15-week abortion ban in *Dobbs v. Jackson Women's Health Organization*.[139] The case, which overturned *Roe v. Wade*, opened the door for subsequent fights about the right to a legal abortion and the weight the law puts on fetal tissue.[140] As will be described below, reopening questions about cell ownership could create a feedback loop further limiting access to abortion, because anti-abortion activists use fetal personhood as an argument for total abortion bans.[141]

Based on a California Supreme Case that has been cited more broadly, currently, research participants do not retain property rights to cells or other biological tissues donated for research.[142] John Moore brought a conversion lawsuit against the University of California where he alleged that the University and his doctor had benefited financially from a cell line derived from his spleen cells.[143] Specifically, Moore "theorize[d] that he continued to own his cells following their removal from his body, at least for the purpose of directing their use, and that he never consented to their use in potentially lucrative medical research."[144] The court denied Moore's conversion claim on both legal and practical grounds.[145]

Despite *Moore* never having been overruled, research participants who find out about misuse of samples could advance claims to regain property rights under a different line of precedent. In cases concerning reproductive tissues, such as eggs, sperm, and embryos, courts have decided not to apply the *Moore* standard for ownership of excised cells.[146] Given the number of similarities (described in

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138 *See, e.g.*, Moore v. Regents of Univ. of Cal., 51 Cal. 3d 120, 141 (1990).

139 Dobbs. v. Jackson Women's Health Org., 142 S.Ct. 2228, 2284-85 (2022).

140 *See* Harry I. Black, *3 Takeaways About Abortion Litigation Since Dobbs*, BRENNAN CTR. FOR JUST. (Dec. 8, 2022), https://perma.cc/ZGT4-24YQ.

141 *See* Wendy Davis, *The Next Big Battle in America's Abortion Fight will be Over Fetal Personhood*, NBC NEWS (Oct. 23, 2022), https://perma.cc/8ZCR-FFE2.

142 *See Moore*, 51 Cal. 3d at 136-37. *Moore* is highly persuasive in other courts. According to Lexis, it has been cited in over 1,200 state and federal court decisions.

143 *Id.* at 125-28. *Moore* also brought a breach of informed consent claim. In this case, the court recognized a duty of care between *Moore* and his doctor. The *Greenberg* court distinguished *Moore* because the doctor maintained a clinical relationship with Moore and the researchers in *Greenberg* were "solely medical" researchers." *See* Greenberg v. Miami Children's Hosp. Rsch. Inst., Inc., 264 F. Supp. 2d 1064, 1070 (S.D. Fla. 2003).

144 *Moore*, 51 Cal. 3d at 134-35.

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> There are three reasons why it is inappropriate to impose liability for conversion based upon the allegations of Moore's complaint. First, a fair balancing of the relevant policy considerations counsels against extending the tort. Second, problems in this area are better suited to legislative resolution. Third, the tort of conversion is not necessary to protect patients' rights. For these reasons, we conclude that the use of excised human cells in medical research does not amount to a conversion.

Id. at 142-43.

146 Obasogie, *supra* note 9, at 53.

Section I) between stem cell-based embryo models and embryos resulting from fertilization, courts may analogize stem cell-based embryo models to preembryos stored after IVF.[147] Of particular importance, stem cell-based embryo models—like frozen preembryos—maintain life potential.

Reasoning used in embryo custody cases can help us understand how courts may classify stem cell-based embryo models. In a heavily cited case on the property status of human preembryos, *Davis v. Davis*, the court articulated a new standard because preembryos, "deserve[] respect greater than that accorded to human tissue but not the respect accorded to actual persons."[148] The *Davis* case arose from a divorce dispute between Junior Lewis Davis and Mary Sue Davis.[149] The pair disagreed over the ownership of frozen embryos prepared for IVF during their marriage.[150] While Mary wanted to donate the embryos to an infertile couple, Junior "preferred to leave the embryos in their frozen state until he decided whether or not he wanted to become a parent outside the bounds of marriage."[151] The court concluded, "preembryos are not, strictly speaking, either 'persons' or 'property,' but occupy an interim category that entitles them to special respect because of their potential for human life."[152] Under this standard, the court advised other courts to first look to a contract over the disposition of embryos. If no contract exists, a court should weigh the relative interests of the parties in using or not using the preembryos.[153] In *Davis*, the court held that Junior's interest in avoiding genetic parenthood outweighed Mary Sue's interests.[154]

Since the *Davis* decision, several courts across the country have interpreted the *Davis* "special respect" standard for disputes over the ownership of frozen preembryos.[155] Although courts have adopted a variety of approaches to interpret

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147 In a recent order, Judge Kacsmaryk uses the term "unborn human" to refer to the medical effects of mifepristone on 7-week-old fetuses. All. for Hippocratic Med. v. U.S. Food & Drug Admin., No. 2:22-CV-223-Z, 2023 WL 2825871, at *1 (N.D. Tex. Apr. 7, 2023) *aff'd in part, vacated in part*, 78 F.4th 210 (5th Cir. 2023). This dictum demonstrates a move toward fetal personhood that could extend to cover stem-cell based embryo models.

148 Davis v. Davis, 842 S.W. 2d 588, 596 (Tenn. 1992). The *Davis* decision has been cited and interpreted widely. *See infra* note 158, citing cases.

149 *Id.* at 589.

150 *Id.*

151 *Id.* at 589-90; Obasogie, *supra* note 9, at 61.

152 *Davis*, 842 S.W. 2d at 597 (emphasis added).

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> Ordinarily, the party wishing to avoid procreation should prevail, assuming that the other party has a reasonable possibility of achieving parenthood by means other than use of the preembryos in question. If no other reasonable alternatives exist, then the argument in favor of using the preembryos to achieve pregnancy should be considered. However, if the party seeking control of the preembryos intends merely to donate them to another couple, the objecting party obviously has the greater interest and should prevail.
>
> *Id.* at 604.

154 *Id.*

155 *See, e.g.*, In re Estate of Kievernagel, 83 Cal. Rptr. 3d 311, 315-16 (Ct. App. 2008); Hecht v. Superior Court, 20 Cal. Rptr. 2d 275, 283 (Ct. App. 1993); Jocelyn P. v.

the special respect standard, "each approach attempts to resolve disputes between progenitors by emphasizing different policies: the progenitors' autonomy in deciding the fate of preembryos created with their own gametic material, the reality that progenitors may change their minds as time passes, or both."[156]

In addition to weighing the parenthood interests of both parties, the *Davis* court discussed the major ethical debate around the human status of a frozen preembryo.[157] In applying the *Davis* decision, many courts avoid the ethical debate by attributing their decisions to a party's right to procreational autonomy.[158] For example, in *A.Z. v. B.Z.*, the Supreme Judicial Court of Massachusetts held that an ex-husband's interest in avoiding procreation outweighed his ex-wife's interest in having additional children.[159] The Supreme Court of New Jersey also engaged in a discussion of the fundamental nature of procreational rights in reviewing an appellate decision ordering the destruction of seven preembryos after J.B. and M.B. divorced.[160] The Court ultimately held that the interests of both parties should be evaluated, but "the party choosing not to become a biological parent will prevail."[161]

Unfortunately, courts' reliance on the right to procreational autonomy does

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Joshua P., 250 A.3d 373, 444, 467 (2021); In re Marriage of Witten, 672 N.W.2d 768, 776-79 (Iowa 2003); J.B. v. M.B., 170 N.J. 9, 29 (2001).

156 Bilbao v. Goodwin, 333 Conn. 599, 608 (2019). The different approaches also refer to the overall approach courts have taken with regard to party pre-contracts and current opinions. The Superior Court of Pennsylvania categorized the jurisdictional approaches in preembryo cases into three types of analysis: contractual approach, the contemporaneous mutual consent approach, and the balancing approach. The approaches recognize prior written contracts to a varying degree. *See* Reber v. Reiss, 42 A.3d 1131, 1134-36 (Pa. 2012).

157 *Davis*, 842 S.W. 2d at 156-57.

158 *See, e.g.*, A.Z. v. B.Z., 431 Mass. 150, 162, (2000); In re Marriage of Rooks, 429 P.3d 579, 581 (Colo. 2018); McQueen v. Gadberry, 507 S.W.3d 127, 145 (Mo. Ct. App. 2016); *J.B.*, 170 N.J. at 22-23.

159 *A.Z.*, 431 Mass. at 159-62.

160 *J.B.*, 170 N.J. at 22-23. The court noted that both parties, as well as the ACLU Amici, advocated for the court to consider the right to privacy over procreational decisions. The United States Supreme Court invoked and secured procreational rights in Skinner v. Oklahoma, 316 US 535, 541 (1942) (forced sterilization), Griswold v. Connecticut, 381 US 479, 485-86 (1965) (contraceptives), and Eisenstadt v. Baird, 405 U.S. 438, 453 (1972) (same).

161 *J.B.*, 170 N.J. at 30. Scholars have disagreed with many of the courts' choices to focus these cases on the "the right not to be a parent." For example, I. Glenn Cohen argues that courts should deconvolute parenthood into the right not to be a gestational parent, the right not to be a genetic parent, and the right not to be a legal parent. Cohen argues for upholding pre-contracting of genetic parenthood rights and without a contract the default should be to avoid reproductive use of frozen embryos with exceptions when a party is unable to have another genetic child. *See* I. Glenn Cohen, *The Right Not to Be A Genetic Parent?*, 81 S. CAL. L. REV. 1115, 1121-22, 1196 (2008). The right not to be a parent extends to cases over gametic material such as donated sperm. Harvey L. Fiser and Paula K. Garrett criticize court decisions that give sperm cells special treatment compared to other bodily tissues because of their potential for human life. The authors characterize the courts' view as "life begins at ejaculation." *See* Fiser & Garrett, *supra* note 107, at 39-41.

not translate to a court decision about stem cell-based embryos used for research, because the result of the research is not traditional parenthood. Thus, in the event of a dispute over ownership of a stem cell-based embryo model, courts may have to engage in the broader ethical debate around the start of human life.[162]

Although the Supreme Court did not opine on fetal personhood in *Dobbs*,[163] experts agree that statutes and case law are likely to develop in this area as a result of the decision.[164] Through dicta in both the district court and appellate decision in *Alliance for Hippocratic Medicine, et al. v. U.S. Food and Drug Administration, et al.,* judges have begun to embrace the idea of fetal personhood–[165] the belief that fetal tissue has all of the rights guaranteed under the Constitution, including that to life.[166] In this case against the Food and Drug Administration (FDA) challenging the approval of a drug used for medical abortions (mifepristone),[167] district court Judge Kacsmaryk, stayed the FDA approval of the drug for subsequent proceedings, but repeatedly referred to embryos and fetuses as "unborn humans" in his decision and explained the decision to use such language in the first footnote.[168] The Appellate Court adopted similar language to refer to fetal tissue affected by mifepristone.[169] A statute or judicial finding for fetal personhood may open the door for research participants to bring suits against researchers and research institutions. In a parallel situation, a conservative plaintiff and judge may see stem cell-based embryo model research as a step forward in a fight for fetal personhood. The need for researchers to treat all embryonic tissue, including stem-cell based embryo models as human lives, would limit how researchers could create, treat, and dispose of research specimens. Fetal personhood laws would have negative impacts beyond research labs, such as by limiting access to in vitro fertilization or emergency contraception, so scientists should do what they can to prevent judicial decisions on the status of stem cell-based embryo models.[170]

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162 *See Davis*, 842 S.W. 2d at 596-97.

163 *Dobbs*, 142 S. Ct. at 2261 ("Our opinion is not based on any view about if and when prenatal life is entitled to any of the rights enjoyed after birth.").

164 *See* Madeleine Carlisle, *Fetal Personhood Laws Are a New Frontier in the Battle Over Reproductive Rights*, TIME (Jun. 28, 2022), https://perma.cc/K36E-D8NL.

165 All. for Hippocratic Med. v. U.S. Food & Drug Admin., 2023 U.S. Dist. LEXIS 61474, at *4 (N.D. Tex. Apr. 7, 2023), *aff'd in part*, *vacated in part*, U.S. App. LEXIS 21630, at *52 (5th Cir. 2023), *cert. granted sub nom.* Danco Lab's, L.L.C. v. All. Hippocratic Med., U.S. LEXIS 4916 (U.S. Dec. 13, 2023), and *cert. granted sub nom.* FDA v. All. Hippocratic Med., U.S. LEXIS 4917 (U.S. Dec. 13, 2023), and *cert. denied sub nom.* All. Hippocratic Med. v. FDA, U.S. LEXIS 4914 (U.S. Dec. 13, 2023).

166 *See* Carlisle, *supra* note 164.

167 *All. for Hippocratic Med.*, 2023 U.S. Dist. LEXIS 61474.

168 *Id.* at *4, n.1.

169 *Id.* at *52.

170 *See* Carlisle, *supra* note 164; *see also* H.R.J. Res. 18, 99th Gen. Assemb., 1st Reg. Sess. (Mo. 2017) (proposing ballot measure to redefine "person" to include "every unborn human child at every stage of biological development from the moment of conception until birth."); Planned Parenthood Advocates in Missouri, *Constitutional Amendment: Abortion*

In some states, research participants or organizations fighting against stem cell-based embryo research may find their way into court using an alternative approach, by arguing the research inadvertently breaks cloning laws. We have no reliable evidence of cloned humans,[171] but the birth of a cloned sheep, Dolly, through somatic nuclear transfer in 1997 sparked enough outrage for a governmental response.[172] In 1998, concerned about ethical responsibility and safety, the commissioner of the Food and Drug Administration declared the "FDA had statutory authority to regulate reproductive cloning under the Food, Drug, and Cosmetic Act (FDCA)."[173] Although experts continue to debate whether the commissioner correctly interpreted his authority, the definition of reproductive cloning articulated by the FDA does apply to stem cell-based embryo models, because making the models does not rely on transferring genetic material between cells.[174]

Some state legislatures also took a statutory approach to prevent human cloning.[175] Such laws may prohibit stem cell-based embryo research, because when laws are not sufficiently precise, they may target cloning as well as activity that

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Ban & Fetal Personhood, https://perma.cc/KRD4-HQJK (detailing how fetal personhood would have "have extreme and dangerous consequences.").

171 In 2002, a religious cult called the Raelians announced the birth of the first cloned human baby, Eve. The report has not been independently verified and many do not believe the story is true. *See* Emma Young, *First cloned baby "born on 26 December"*, NEWSCIENTIST, (Dec. 22, 2002), https://perma.cc/HK4H-XBW5; Henry T. Greely, *Human reproductive cloning: The curious incident of the dog in the night-time*, STAT, (Feb. 22, 2020), https://perma.cc/4UQV-J3XX.

172 Greely, *supra* note 171.

173 Kerry L. Macintosh, *Brave New Eugenics: Regulating Assisted Reproductive Technology in the Name of Better Babies*, U. ILL. J. L., TECH. & POL'Y 257, 269 (2010).

174 The Acting FDA Commissioner, Dr. Michael Friedman, announced FDA authority to regulate cloning because it considered human cloning as a form of gene therapy. This suggests that the jurisdiction connected to the act of transferring genetic material from one cell to a another. Richard A. Merrill & Bryan J. Rose., *FDA Regulation of Human Cloning: Usurpation or Statesmanship?,* 15 HARV. J. L. & TECH. 86, 98-99 (2001); *see also* Rick Weiss, *Legal Barriers to Human Cloning May Not Hold Up*, WASH. POST (May 23, 2001), https://perma.cc/4G6N-AK3B ("Many legal scholars say they find little evidence to support the FDA's assertion of authority over cloning. They say food and drug laws provide no legal basis for stopping doctors from trying to clone a person, and if the FDA tried to do so it would lose in court.").

175 Seven states have laws prohibiting cloning-to-produce-children and for cloning-for-biomedical-research. (Arizona, Arkansas, Michigan, North Dakota, Oklahoma, South Dakota, and Virginia). Ten states prohibit cloning-to-produce-children but permit cloning for-biomedical research (California, Connecticut, Illinois, New Jersey, Rhode Island, Maryland, Massachusetts, Missouri, Montana). Minnesota statute prohibits cloning-for-biomedical-research without addressing cloning-to-produce children. *See* The Witherspoon Council, *The Threat of Human Cloning Ethics, Recent Developments, and the Case for Action*, Appendix: State Laws on Human Cloning, NEW ATLANTIS (2015), https://perma.cc/SBK7-PUUH.

regulators do not want to restrict.[176] For example, Arizona Revised Statutes §36-2312 (2010) forbid any "attempt to create an *in vitro* embryo by means other than fertilization through the combination of a human egg with a human sperm."[177] Connecticut law may also bar stem cell-based embryo research because the statute prohibits inducing or replicating "a living human being's complete set of genetic material to develop after gastrulation commences."[178] Connecticut defines gastrulation as the "process immediately following the blastula state when the hollow ball of cells representing the early embryo undergoes a complex and coordinated series of movements that results in the formulation of the three primary germ layers: the ectoderm, mesoderm, and endoderm."[179] Rather than banning the cloning method of transferring genetic material, these imprecise laws regulate broader activity potentially including the development of *in vitro* embryo models. In addition to disputes arising between research participants and researchers, states may bring independent criminal legal action against research institutions for violating these laws.[180]

III. Proposal for Collection of New Material with Dynamic Informed Consent

The previous section outlined some of the ethical and legal problems emerging with the advancement of stem cell-based embryo model technology. Informed consent practices initiate a partnership between researchers and participants that could avoid risking participant autonomy and potential legal problems.[181] The novelties of stem cell-based embryo research call for novel consent approaches to research participation. Rather than relying on practices of broad consent, researchers should follow the plan explained below and collect new biologic material from participants who are fully informed on the researchers' goal to pursue stem cell-based embryo research. Research participants can consent to stem cell-based embryo research studies when they understand the specific goals of a research plan and choose to participate.[182] This section will outline my recommendations for a new approach: collecting specific consent for

176 *See* Henry T. Greely, *Banning "Human Cloning": A Study in the Difficulties of Defining Science*, 8 SO. CAL. INTERDISC. L. J. 131 (1998) (exploring how inaccurate or unclear statutory definitions of cloning lead to a failure of the statutes to regulate activities they intend to regulate).

177 SCR 1044, ARIZ. REV. STAT. §36-2312 (2010).

178 CONN. GEN. STAT. §32-41jj (1989).

179 *Id.*

180 *Id.* (classifying as class D felony)*;* SCR 1044, ARIZ. REV. STAT. §36-2312 (2010) (classifying as a class 1 misdemeanor).

181 By partnership, I am not referring to a legal partnership. As I discussed in Section II.B., courts are reluctant to recognize a legal partnership between researchers and participants.

182 To my knowledge research groups have not used specific consent procedures to inform cell or tissue donors of their intention to create embryo models from iPSCs.

stem cell-based embryo model research at the time of material donation and setting up dynamic consent mechanisms for future work.

A. Previously Collected Cell Lines Should Not Be Used for Stem-cell Based Embryo Research

Researchers often rely on previously collected, banked iPSCs for stem cell-based embryo model research.[183] As illustrated above, researchers rely on the original (and likely inadequate) consent forms. The ISSCR recommends researchers rely on the standard from the original material donation when researchers use banked cells for stem-cell based embryo research.[184]

The ISSCR is not the first or only professional organization to recommend adhering to the consent practices used at the time of collection for banked stem cell lines. In May 2009, the American Association for the Advancement of Science (AAAS) advised the National Institutes of Health (NIH) to apply "stringent informed consent procedures" to the collection of embryonic stem cells supported by federal funding.[185] In the comment, Alan I. Leshner (former Chief Executive Officer for the organization) urged the NIH to "grandfather in" stem cell lines that had previously been collected, following core principles of informed consent.[186] Although the 2009 NIH guidelines did not automatically "grandfather in" stem cell lines, the guidelines created a Working Group of the Advisory Committee to the Director to review the guidelines and to recommend whether individual cell lines should be eligible for NIH funding.[187] Currently, the registry of embryonic stem cell lines includes forty lines available for federally funded research approved initially in December 2009.[188]

The creation of ESC lines from donated embryos provides an optimal case for "grandfathering in" cell lines and relying on original consent. As described above, public debate about embryo research centers on a difference of moral opinions as to when life begins and when/whether embryos may be destroyed.[189] At the time of donation, embryo donors knew their biological material would be

183 In all three examples above, the researchers used banked cell lines. Banked cell lines are cryopreserved and can be unfrozen for future experiments. *See* Rhodes et al., *supra* note 10; Zheng et al., *supra* note 10; Yu et al., *supra* note 2.

184 The International Society of Stem Cell Research, *supra* note 33, at 15.

185 Alan I. Leshner, *Re: Request for Public Comment on NIH Guidelines for Human Stem Cell Research,* AAAS (May 20, 2009), https://perma.cc/6KAC-EER7.

186 *Id.*

187 CONG. RSCH. SERV., RL33540, STEM CELL RESEARCH: SCIENCE, FEDERAL RESEARCH FUNDING, AND REGULATORY OVERSIGHT 18 (2013).

188 I am assuming the December 2009 approved lines were grandfathered in by the original approval committee. *See NIH Human Embryonic Stem Cell Registry*, NIH GRANTS AND FUNDING, https://perma.cc/CL56-ZYVE.

189 *Compare* Address from the Bush Ranch on Stem Cell Research, *supra* note 17, *with* EXEC. ORDER NO. 13505 (Mar. 9, 2009), https://perma.cc/3C65-P89F; *see also* Levin, *supra* note 109.

used for embryo research that may include embryo destruction.[190] Thus, the donors could consider their moral opinions in their decision to donate. The same is not true for donors of material used in stem cell-based embryo model research, making it a suboptimal case for "grandfathering in" cell lines. In the latter case, donors do not have the opportunity to consider the morality of embryo research when deciding whether to participate in the research.[191]

As an alternative to "grandfathering in," researchers could recontact donors for reconsent to turn somatic cell lines or iPSCs into stem cell-based embryo models. Through reconsent, participants can learn about new research plans, consider their opinions on embryo (or embryo model) research, and reaffirm their decision to participate in the research.[192] This practice practically eliminates the possibility that participants feel harmed by a loss of autonomy.

However, practical and ethical issues prevent wide adoption of reconsent practices.[193] As a practical matter, researchers are often unable to recontact research participants. For many studies, researchers intentionally deidentify samples or do not collect such identifiers in the first place, and reidentification may be difficult.[194] Even if researchers did not deidentify samples, participants may have changed their contact information without updating the research team.[195] Reconsent may also raise ethical concerns, because recontacting donors "without their prior permission . . . might be considered an invasion of privacy."[196] To avoid issues with grandfathering cell lines in and seeking reconsent, stem cell-

190 Embryo donation usually takes place in an IVF clinic under the supervision of a physician and donors are offered choices for embryo disposition. *See, e.g.*, CAL. HEALTH & SAFETY §125315 (2018). Researchers could in theory make stem cell-based embryo models from hESCs collected in IVF clinics but this practice would defeat the purposes of using iPSCs to evade ethical challenges of traditional embryo research.

191 *See supra*, Section II.A.

192 D.B. Resnik, *Re-consenting Human Subjects: Ethical, Legal, and Practical Issues*, 35 J. MED. ETHICS 656 (2009).

193 Reconsent is different from dynamic consent because researchers did not anticipate continued communication with research participants and, thus, have not set up the necessary infrastructure.

194 For example, HapMap project did not collect individual information. "Because no individual identifiers are available for any of the newly-collected samples, it will not be possible to recontact donors in the future to seek their consent to other studies." Rotimi et al., *supra* note 69, at 192.

195 Resnik, *supra* note 192, at 656. ("Re-consent may be difficult to implement, due to problems with re-contacting subjects (such as missing or incorrect contact information) or resource constraints (such as insufficient time, staffing, or money)."). For example, Chen, Berkman, and Hull, attempted to contact research participants with a waiver of consent and option to withdraw. Of the original 1,978 participants in a rare-disease research study, the researchers had no contact information for 20 participants and 224 letters returned as undeliverable. Stephanie C. Chen et al., *Recontacting Participants for Expanded Uses of Existing Samples and Data: A Case Study*, 19 GENETICS MED. 883, 885 (2017).

196 Katriina Aalto-Setälä et al., *Obtaining Consent for Future Research with Induced Pluripotent Cells: Opportunities and Challenges,* 7 PLOS BIOLOGY 204, 206 (2009); *see also* Resnik, *supra* note 192, at 657.

based embryo research should only be conducted with newly collected cells.[197] Further details on how researchers should obtain informed consent for newly collected cells are described below.[198]

B. Fresh Tissues and Cells Should Be Used for Stem Cell-based Embryo Model Research

The implementation of new informed consent procedures is relatively easy when researchers collect fresh cells or tissues. Upon collection of new biological material for derivation of both iPSCs and stem cell-based embryo models, researchers can inform research participants of the potential uses of their cells. Fortunately, many research groups are already implementing language about stem cells into their consent practices. For example, the University of Michigan Stem Cell Core consent form discusses iPSC research.[199] Research institutions can explain their intent to create stem cell-based embryo models and add appropriate language, such as the language recommended by the ISSCR, to their forms. The ISSCR recommends that when researchers collect new material, they communicate:

> the fact that an immortal stem cell line could be established that is a partial or full genetic match to the cell or tissue donor and that the stem cell lines could be shared with other researchers outside the institution and jurisdiction for other research purposes that may not be fully anticipated at this time. [200]

For stem cell-based embryo research, scientists should also inform potential research participants that,

> [s]ome stem cell researchers studying early human development or reproduction may want to use stem cells to create … embryos. These . . . embryos would be genetically connected to you. None of the embryos … created from your cells will be used to produce a baby or pregnancy.[201]

Assuming the researchers adequately educate potential donors on the meaning of the scientific research described in this form, the donor can weigh their personal morals and make an autonomous choice to participate in the study.

Specific consent for biological material donation has been employed successfully in contexts such as organ donation. In the United States, the United Network for Organ Sharing (UNOS) operates a system to obtain organs and match donors to individuals in need called the Organ Procurement and Transplant network (OPTN).[202] Individuals can register to be organ donors online or

197 *See infra,* Section III.C (discussing how newly collected cell lines could be used for future work without issues discussed above).

198 *See infra*, Section III.B, III.C.

199 Informed consent document, *supra* note 101.

200 The International Society of Stem Cell Research, *supra* note 33, at 17 (Recommendation 2.3.2.3).

201 *Id.* at 9 (Appendix 2. Sample form A2.2).

202 *Organ Donation Legislation and Policy,* HEALTH RES. & SERVS. ADMIN. (Apr. 2021), https://perma.cc/7PQ8-VJFT.

at their local motor vehicle department.[203] Alternatively, their families can consent once they are deceased.[204]

The relatively general standards for organ donation changed after doctors performed the first face transplant in 2007.[205] In comparison to donation of internal organs, potential donors and families question face transplants due to the highly personal connection people have to their facial structure.[206] Recognizing the uniqueness of a face compared to other organs, the OPT-IN policy requires specific consent for face donations.[207] Like specific consent for stem cell-based embryo model research, additional specific consent for face donations ensures donors specifically consider that potential use of their tissue and make informed, autonomous choices.

C. Stem Cell-based Embryo Model Researchers Should Employ Dynamic Consent Models to Preserve the Possibility of Future Research

Scientists and the general research community benefit from cell lines collected with broad consent.[208] Thus, researchers may prefer an informed consent model for stem cell-based embryo research that also allows for future uses and sharing of cell lines.

The ISSCR guidelines recommend obtaining consent for future work by creating consent forms that acknowledge the possibility that potential uses for donated biological material "may not be fully anticipated at this time."[209] Around fifteen years ago, scientists could not reprogram somatic cells into stem cells, and just six years ago, we could not create integrated embryo models with iPSCs.[210] Given the speed of innovation, we may reach new crossroads similar to the one we face now with stem cell-based embryo models if we continue to allow consent for future, unanticipated work. As an alternative approach, researchers should set up dynamic consent models for cell lines that can be used for potentially controversial research, including stem cell-based embryo model research.

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203 *How To Sign Up,* HEALTH RES. & SERVS. ADMIN. (Sept. 2021), https://perma.cc/EP2Z-XKJ8.

204 *Donating Organs after Death,* BETH ISRAEL LAHEY HEALTH, (2012), https://perma.cc/5D9Z-LKZY.

205 *What Can be Donated*, HEALTH RES. & SERVS. ADMIN. (SEPT. 2021), https://perma.cc/YPT5-QFJR.

206 Brendan Parent, *Faces as Organ Donations: Who has the Last Word?*, 44 HASTINGS CTR. REP., Nov.-Dec. 2014 at 93.

207 *Id.*

208 *See, e.g.*, *supra* note 73 (citing examples of multiple papers using the same cell lines).

209 The International Society of Stem Cell Research, *supra* note 33, at 17.

210 *See* Takahashi et al., *supra* note 18 (announcing the creation of iPSCs from somatic cells in 2007); *see also* Janet Rossant & Patrick P.L. Tam, *Opportunities and Challenges with Stem Cell-based Embryo Models*, 16 STEM CELL REPS 1031, 1032 (2021) (reviewing the first studies to create integrated embryo models in 2017 at the earliest).

Dynamic consent models use modern technology to allow research participants to consent to future uses of donated biological material privately.[211] Dynamic consent provides the benefits of recontact without the privacy and ethical risks described above. When researchers enroll participants for stem cell-based embryo model research, they could explain the potential for future controversial uses of the cells and set expectations for recontact procedures.[212] This approach should be used for unorganized, nonintegrated, and integrated models. Recontact should take place when new research falls outside the time frame and subject matter of the original work, or when researchers choose to share cell lines more broadly.[213]

Clinical research projects and commercial genome sequencing efforts have implemented dynamic consent models to provide research participants control over their data.[214] Patients and patient representatives advocate for dynamic consent models for clinical trials because research participants no longer want to be "passive observers and sources of research data."[215] A greater sense of involvement will also strengthen the trust research participants have in science and in the researchers they interact with.[216] In a qualitative research study evaluating biobank participants' views on dynamic consent structures, participants "were enthusiastic about the potential to know more about the research process and how their samples were being used."[217]

Given the participant-centered benefits described above, some may ask why

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211 *See* Fika K. Dankar et al., *Informed Consent in Biomedical Research*, 17 COMPUTATIONAL & STRUCTURE BIOTECHNOLOGY J. 463, 469-70 (2019).

212 The expectation for recontact could be based on the level of controversy around a particular type of research. Scholars have recommended including a controversial criterion in broad consent forms. The clauses exclude research with the potential to lead to discrimination or that goes against "established cultural or religious traditions, beliefs[.]" Zubin Master & David B. Resnik, *Incorporating Exclusion Clauses into Informed Consent for Biobanking*, 22 CAMBRIDGE Q. HEALTHCARE ETHICS 203, 206 (2013) (advocating for exclusion clauses in biobank consent forms and presenting the pros and cons of the practice).

213 My proposal for dynamic consent centers on individuals rather than groups. In some cases, consent from a group may be necessary. For example, when a study focuses on genetic diversity or community health such as with the HapMap project or the Havasupai research program the consent conversations should involve many members of the group. While in these cases individuals can make their own choice to interact with researchers, the information learned from the studies will reveal information about the group. Other scholars have discussed when group consent should be implemented. *See*, *e.g.*, Henry T. Greely, *The Control of Genetic Research: Involving the "groups between"*, 33 HOUS. L. REV. 1397, 1415-20 (1997).

214 *See* Dankar et al., *supra* note 211, at 470.

215 Charlotte J. Haug, *Whose Data Are They Anyway? Can a Patient Perspective Advance the Data-Staring Debate?,* 376 NEW ENGLAND J. MED. 2203, 2204 (2017).

216 *See* Dorit T. Stein & Sharon F. Terry, *Reforming Biobank Consent Policy: Necessary Move Away from Broad Consent Toward Dynamic Consent*, 17 GENETIC TESTING & MOLECULAR BIOMARKERS 855, 855-56 (2013).

217 Harriet J.A. Teare et al., *Towards 'Engagement 2.0': Insights from a Study of Dynamic Consent with Biobank Participants*, 1 DIGIT. HEALTH 1, 11 (2015).

researchers have not begun to implement dynamic consent models for most biological tissue donation, and specifically for stem cell research. Dynamic consent models raise concerns for researchers and research institutions. Researchers do not want to update protocols or consent models. Researchers already spend more time than they would like on administrative tasks,[218] and researchers often feel increasing IRB review procedures can create "an unnecessary 'burden'" because they delay research and add financial burdens that do not increase participant protections.[219] As a result, researchers rely heavily on previously collected cell lines and previously collected data for answering complex scientific questions.[220] In some fields and at some institutions, a new system may prohibit innovation because the research centers do not have the funding to create and maintain systems.

Beyond the classic concerns that accompany any new systems, such as constraints on time and money, the successful implementation of dynamic consent models depends on research participants' technological access and literacy.[221] Researchers have called this a "digital divide," because older participants or those in remote communities may not have access to the tools that facilitate reconsent.[222] These obstacles can hopefully be mitigated through innovative design strategies and global increases in access to the internet.[223]

Aside from technical problems, critics of dynamic consent worry about what they call "consent fatigue."[224] If participants are continuously asked to consent

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218 *See* Adam James, *Too many tasks*, 475 NATURE 257 (2011) (arguing the administrative tasks principal administrators must complete unfairly distract from the reasons young people pursue careers in academic science); Rebecca Trager, *Almost half of US Researcher's time goes on admin*, CHEMISTRY WORLD (Sep. 8, 2014), https://perma.cc/R5CJ-VCB8 (reporting on a National Academies survey of scientists that found they spend, on average, 42% of their time on administrative tasks); National Science Foundation, No. NSB-14-18, Reducing investigators' administrative workload for federally funding research (Mar. 10, 2014), https://perma.cc/2TMQ-8BZZ (outlining methods to reduce administrative work).

219 George Silberman & Katherine L. Khan, *Burdens on Research Imposed by Institutional Review Boards: The State of the Evidence and Its Implications for Regulatory Reform*, 89 MILBANK Q. 599, 601 (2011).

220 *See, e.g.*, *supra* note 73 (citing examples of multiple papers using the same cell lines).

221 Megan Prictor et al., *Equitable Participation in Biobanks: The Risk and Benefits of a "Dynamic Consent" Approach*, 6 FRONTIERS PUB. HEALTH 1, 4 (2018) ("This is often cited as a 'digital divide,' with focus (perhaps unfairly) on older generations. However, it could equally apply to communities, for instance in remote parts of Australia, that lack access to technology, or reliable infrastructure including Wifi networks to allow meaningful reliance on these tools").

222 *See* Jane Kaye et al., *Dynamic Consent: A Patient Interface for Twenty-first Century Research Networks,* 23 EUR. J. HUM. GENETICS 141, 143 (2015); Prictor et al., *supra* note 221.

223 Kaye, *supra* note 222, at 143 (identifying cellular-based tablets as a potential solution).

224 *See* Mark Sheehan et al., *Authority and Future of Consent in Population-Level Biomedical Research*, 12 PUB. HEALTH ETHICS 225, 228 (2019).

to new research projects, they may stop engaging—either by consenting without considering the pros and cons of the new work, or by withdrawing completely from the program.[225] For cell and tissue research, researchers can avoid these problems by grouping research practices. For example, rather than having donors consent to each study, donors could consent to groups of studies by type–unorganized, nonintegrated, and integrated model research. The practice would decrease the number of times the researcher must recontact the participant while still allowing the participant to choose how their material is used. If researchers continue to think critically about effective groupings of research methods, the participants will not be overwhelmed. Further, by allowing participants to consent to material sharing, researchers from multiple institutions will still be able to benefit from the cellular resources.

Critics of dynamic consent worry about efficiency and allocation of the public resources that fund basic and clinical research.[226] The recommendations presented in this Note do not, however, advocate for all biological sample collection to implement dynamic informed consent practices.[227] Rather, they suggest that when potential cellular or data usages cross into a controversial research area, the benefits of dynamic informed consent outweigh the costs.[228] When implemented effectively, dynamic informed consent ensures participant autonomy in research, resulting in enthusiastic and involved research participants who will more likely communicate their moral or ethical concerns with researchers, rather than pursue legal action. Thoughtful and specific implementation of dynamic informed consent alleviates concerns that implementation of the recommendations presented in this Note will stall biological innovation or misuse public funding.

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225 *Id.*

226 *See, e.g.*, Haug *supra* note 215.

227 Deciding which types of research should cross the controversy line requiring dynamic consent depends on a range of factors. Answering this question for a new research avenue would take a complex balancing of some of the risks and participant attitudes explored for this topic above. It may also require deciding on a threshold for the percent of people in a community who would be upset if they learned how their material was being used. Depending on the scope of the project, the threshold may need to be low to prevent negative consequences. For example, dynamic informed consent may have prevented the lawsuits brought by small groups of families in Minnesota and Texas for lack of written informed consent which had large impacts on public health research. In each case the states had used deidentified leftover bloodspots from the state's public newborn screening program for research. The settlements in the cases resulted in the destruction of 1.1 million blood spots in Minnesota and 5.3 million in Texas. *See* Lorna Benson, *After Settlement, Minn. to Destroy 1.1M Newborn Blood Samples*, MPRNEWS (Jan. 13, 2014), https://perma.cc/2HX2-JXVF?type=image (Minnesota story); Peggy Fikac & Austin Bureau, *State to destroy newborn's blood samples,* CHRON (Dec. 22, 2009), https://perma.cc/4ADS-A2LN (Texas story).

228 While I am grouping all stem cell-based embryo model categories for this proposal, I concede that a reasonable person may disagree with this assessment. Some may believe that dynamic consent is not necessary for unorganized models (or even non-integrated models) because the line they draw is on the potential for life. I have decided not to differentiate here, because I foresee many researchers starting with unorganized models and quickly advancing their research questions through experiments with more complex models.

By collecting new biological samples with specific consent for stem cell-based embryo model research and implementing dynamic consent for future research, researchers avoid threatening participant autonomy or breaching consent when they later expand research projects. First, robust informed consent practices return autonomy to research participants because participants will make an educated choice on whether to donate biological material for the research. Second, when research subjects have specifically consented to research, they are more informed research participants and are less likely to pursue legal action.[229] Finally, if legal action does arise, specific consent practices provide a legal contract for courts to interpret, thereby reducing the need for judges to determine life status of the embryo models.[230]

Scientists may also criticize the outlined approach because they would not be able to incorporate previously collected data into stem cell-based embryo model research. However, as the cost of specific analysis practices such as sequencing decreases and the possibility to collect multiple data types at the same time increases, the inability to rely on previously collected data becomes less of a problem.[231] Further, new cell lines collected under the consent model described can quickly become a new, more ethical resource.[232]

CONCLUSION

In this Note, I suggest adopting novel consent practices for stem cell-based embryo model research. In Section I, I outlined the scientific discoveries that led to the development of stem cell-based embryo models. I then explained the three

229 The Havasupai tribe brought legal action for the secondary research that they did not approve of, not the previously disclosed and consented to diabetes research. *See* Havasupai Tribe v. Ariz. Bd. of Regents, 220 Ariz. 214, 218 (Ariz. Ct. App. 2008). In parallel contexts, the plaintiffs in *Moore v. Regents of Univ. of Cal.* and *Greenberg v. Miami* brought legal action because the clinicians used biological material in ways previously not considered by the patients.

230 *See supra*, Section II.B.

231 Cost to sequence a human genome has decreased from almost $100,000,000 in the early 2000s to below $1000 in 2021, *see DNA Sequencing Costs: Data,* NAT'L HUM. GENOME RSCH. INST., https://perma.cc/CV4D-WWQQ. Research protocols now exist to measure both gene expression levels and other molecular phenotypes in the same sample or even the same cell. For example, we can measure gene expression and chromatin accessibility in the same cell. Not only does this reduce the cost of recollecting data, it also eliminates issues with combining data such as correcting for technical differences between two studies. *See* Lia Chappell et al., *Single-Cell (Multi)omics Technologies*, 19 ANN. REV. OF GENOMICS & HUM. GENETICS 15, 30 (2018).

232 The International Society of Stem Cell Research, *supra* note 33, at 9. (Appendix 2. Sample form A2.2). From a conversation with Michael Snyder, the Stanford W. Ascherman Professor in Genetics on 11/19/21. After hearing my proposal for specific consent for stem cell based embryo model research, Dr. Snyder remarked that this will lead to researchers abandoning older cell lines in favor of newly collected and consented for lines. We discussed how this will be a good development for the field as long as the new lines represent a diverse sample of the population.

categories of stem cell-based embryo models by highlighting three recent scientific publications. Finally, I discussed current practices to protect subject autonomy in human subject research and the most recent proposed guidelines for stem cell-based embryo research. In Section II, I presented the bioethical and legal problems with sticking to the status quo of consent models. Finally, in Section III, I proposed collecting new biological materials and setting up dynamic consent for future research.

This discussion only starts a dialogue about the relationship between biological material donors and scientists pursuing stem cell-based embryo model research. This Note intentionally omits several additional technologies often deployed in stem cell-based embryo model research. For example, creation of stem cell-based embryo models from iPSCs derived from multiple species (chimera research) or with germline genetic mutations. Each of these research practices presents additional ethical and legal concerns, such that the ISSCR created a separate category for these models with additional safeguards.[233] As the technologies mature, we will also need to think creatively about the relationships between research participants and scientists. We will need to ask when informed consent is the correct safeguard or if the impact on future generations means we need to rethink our traditional views on autonomy in research participation.

As of now, the scary headline, "We made babies from only skin cells!" remains hyperbolic.[234] The technologies that will make the headline a reality, by contrast, are not fictional. As technology develops and laws describing fetal personhood change, we need to address the legal and ethical problems as they arise – even before the publication of a seemingly science fiction headline. Specific informed consent for stem cell-based embryo research and dynamic consent for future studies ensure research participant autonomy and, hopefully, prevent complicated legal disputes.

233 The technologies are in category 3A (Not allowed; currently unsafe) and 3B (Not allowed; lacks compelling scientific rationale or is ethically concerning). The International Society of Stem Cell Research, *supra* note 33, at 9.

234 This refers to the fictional headline in the introduction. *See* Murray, *supra* note 1.