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Ethics in embryo research: a position statement by the ASRM Ethics in Embryo Research Task Force and the ASRM Ethics Committee

Ethics in Embryo Research Task Force and Ethics Committee of the American Society for Reproductive Medicine

American Society for Reproductive Medicine, Birmingham, Alabama

Scientific research using human embryos advances human health and offspring well-being and provides vital insights into the mechanisms for reproduction and disease. Research involving human embryos is ethically acceptable if it is likely to provide significant new knowledge that may benefit human health, well-being of the offspring, or reproduction. (Fertil Steril® 2020;113:270–94. ©2019 by American Society for Reproductive Medicine.)

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STATEMENT OF PURPOSE AND RECOMMENDATIONS

The American Society for Reproductive Medicine (ASRM, "the Society") is a multidisciplinary organization dedicated to the advancement of the science and practice of reproductive medicine. The Society pursues its mission through the support of education, advocacy, and research that advances the well-being of all reproductive medicine stakeholders, including patients, health care providers, researchers, and the public. As part of its most recent strategic plan, ASRM highlighted the need to "spearhead the agenda for research in reproduction and the development of both the current and future generations of clinical investigators in the reproductive sciences" (1, 2). In an effort to operationalize this goal, the ASRM Research Institute was founded with a mission to guide and support research in the field of reproductive medicine. Cognizant that research in reproductive medicine can involve human embryos, in 2017 the ASRM Board of Directors established the Ethics in Embryo Research Task Force (the "Task Force") to consider, debate, and ultimately draft the present position statement addressing ethical considerations in embryo research. The Task Force's efforts were to include ongoing consultation with the ASRM Ethics Committee (the "Ethics Committee"), a multidisciplinary group established over 30 years ago to provide guidance on ethical issues arising in the field of reproductive medicine. This position statement is a product of the collaboration between the Task Force and the Ethics Committee.

The Task Force is composed of clinicians, researchers, embryologists, medical students, ethicists, and legal experts who gathered beginning in January 2018 via a series of conference calls and email discussions to formulate the structure and substance of its consensus position. While this position statement represents a consensus view of the Task Force, Ethics Committee, and ASRM Board of Directors, the Society acknowledges that it may not be in accord with the views, perspectives and practices maintained by each member of ASRM. Diversity of viewpoint and respect for differing sensibilities are highly respected values at ASRM. As such, the Society encourages its members and members of the public to add their voices to the public discourse on ethics in embryo research in order to enhance the debate over this vital topic of potentially enormous societal impact. This position statement is not an ethical rule adopted by the Ethics Committee and is not part of the organization's code of conduct. It does, however, represent the considered judgment of a number of professionals in reproductive medicine. The Task Force believes that this discussion will be useful to all stakeholders in reproductive medicine as they make individual judgments in this area.

What follows is a discussion of the ethical, legal, historic, and clinical underpinnings of conducting research involving human embryos. The Task Force believes that each of these threads contribute important elements to the overall approach adopted in this position statement. In formulating its approach, the Task Force aspired to provide reasoned analysis and concrete guidance that advances the science and practice of reproductive medicine. As a result of its collaborative efforts, the Task Force makes the following statements:

- Scientific research using human embryos advances human health and offspring well-being, and provides vital insights into the mechanisms for reproduction and disease.
- Many important scientific questions regarding human reproduction, development, fertility and regenerative medicine can only be answered by research involving human embryos.
- Embryo research, with either existing embryos or those produced specifically for research purposes, is ethically acceptable as a means of obtaining new knowledge that may benefit human health, offspring well-being, or reproduction provided certain guidelines and safeguards are followed.
- As with all research using scarce resources, the number of embryos produced or utilized in the research should not exceed the amount needed to answer the research question.
- In order to establish parameters for investigating questions of human development, reproduction, and fertility, it is critical that scientists and society at large work to obtain an understanding of which research questions might best be answered by studying embryos and which can be investigated through other means.
- Embryo research with reproductive intent is research that is conducted with the goal of transfer into the uterus, pregnancy and childbirth, and should only be undertaken after pre-clinical research demonstrates acceptable levels of safety and efficacy. Embryo research with the intent of achieving a viable pregnancy should only be undertaken with the intent of improving health or well-being of the offspring or allowing for reproduction when no other reasonable or feasible alternatives exist or the innovation offers a significant advantage over existing alternatives. Any such research should occur under the auspices of an IRB and include a procedure for reporting on the health and well-being of first-generation offspring, as well as delineate a mechanism for continued follow up over multiple generations.

- Research involving germline gene-editing technologies raises unique issues, given that alterations introduced into the germline may persist for generations. This contrasts with preimplantation genetic testing and other forms of embryo research in which no genetic manipulation is undertaken. Benefits of germline gene-editing technologies include the possibility that the techniques may increase the efficiency of in vitro fertilization such that more embryos are available for reproductive purposes. Research into germline gene editing should establish safety and efficacy before these technologies are used for reproductive purposes.
- Under no circumstances should embryos be used in research without the prior written informed consent of the gamete providers. Consent may be obtained either prior to or after the provision of gametes. Embryos initially produced with reproductive intent using donor gametes may be donated for research so long as express written consent was given by the gamete providers or the individual(s) to whom the gamete providers gave dispositional and decisional control.
- Donors providing their gametes for the purpose of producing embryos for research are entitled to be fully informed about the potential risks and benefits associated with their donation, including those associated with gamete procurement.
- At the time of embryo donation to research not intended to result in reproduction, the donors (or those individuals granted dispositional control by the donors) formation may provide broad consent for research using these embryos, but should be given as much information about the proposed research as is available. This includes consent for the development of stem cell lines and for research that has not yet been identified or conceptualized at the time of the donation. Embryo donors should be aware that stem cell lines derived from their embryos may be stored indefinitely and used for multiple research projects and be shared among more than one investigator. Consent for research at an earlier time, including at the time embryos are produced or subsequently when a decision to donate supernumerary embryos is made, is sufficient.
- If research has reproductive intent, explicit written informed consent from the gamete or embryo donors must be obtained and broad consent is insufficient. Embryos initially produced for personal (non-research) reproductive purposes using donor gametes may be donated for research with reproductive intent so long as the gamete providers either provided express written consent for such use or delegated all decisions regarding research, including research with reproductive intent, to the intended parent(s). Researchers should seek contemporaneous consent from those with dispositional authority over embryos when research has reproductive intent.
- It is the considered judgment of the Task Force that individuals donating embryos that were originally produced with reproductive intent should not be paid as an enticement to make their embryos available for scientific investigation. In so doing, the Task Force acknowledges that individuals may reach different conclusions on this subject and that certain existing research protocols may provide for some form of compensation, including reimbursement for storage fees incurred prior to the provision of embryos for research purposes. The Task Force sets forth the reasoning supporting its judgment, but recognizes that individuals will need to make their own respective decisions in this area. The Task Force's aim is to explicate the issues that it believes individuals should consider in making those determinations.
- The formation of human embryos expressly for research purposes is ethically acceptable so long as the proposed research is consistent with the ethical recommendations set out in this position statement. Payment to egg and sperm donors who produce gametes solely for research purposes is ethically acceptable in the same manner as other human subject research participants are compensated for such participation.
- Embryo and gamete donors should be informed that the research performed using embryos and gametes that they donate may not produce results that will directly benefit them. When possible, and if known, the specific research project, the source of funding, the potential commercial value of the research, and anticipated clinical applications should be disclosed to embryo and gamete donors.
- All efforts should be made to protect the confidentiality and privacy of the embryo and gamete donors. However, given the growing ability to match individuals with their genetic samples, donors should be aware that anonymity cannot be absolutely guaranteed into the future. As part of the consent process, donors should be counseled that genetic information gained from research on embryos may affect the donors, their family members, and their offspring.
- Blanket federal regulations that prohibit: 1) research on existing embryos 2) the formation of embryos and/or embryonic stem cell lines for the purpose of research or 3) funding for research involving human embryos, should be replaced by guidelines that allow for ethically undertaken research. Such guidelines should ideally be formed by a consortium of scientists, ethicists, and other stakeholders and should be based on scientific facts free of bias. Mechanisms for the public to weigh in on the creation of these guidelines should be developed. These guidelines should be periodically updated as dictated by advances in scientific understanding.
- Given the complex ethical issues surrounding the study of human embryos, oversight of the research process is essential. ASRM recommends use of the Common Rule/IRB framework for research involving embryos, even when the facility conducting the research falls outside of structures in which the framework is legally required. Oversight in a consistent fashion across all facilities is thus recommended.
- Public education is important to allow for broad engagement regarding acceptable current and future embryo research directions. Mechanisms of disseminating accurate and timely information regarding the state of embryo research should be developed. Ideally, public funding should be made available for such educational programs.

I. FIRST CONSIDERATIONS: THE STATUS OF THE EMBRYO IN THE RESEARCH SETTING

The need and desirability of scientific research that advances human health, well-being and reproduction is integral to a just society, and increasingly those advances are emerging from research on human embryos. In the four decades since human embryos could be produced and maintained outside the body, the moral and legal status of preimplantation embryos has been debated with an eye toward shaping the conduct of third parties who interact with these developing entities. The need for clarity and consensus grows as scientific inquiry advances, offering tremendous insight into the building blocks of human development and disease. A first priority in shaping the ethical parameters surrounding human embryo research is to clearly set out the methodology and basis for any conclusions or positions adopted that helped shape the Task Force's recommendations.

Language shapes perception. This adage has guided the Task Force in its deliberations and drafting to carefully consider the structure and selection of language used throughout this statement. Striving to employ neutral terms and text whenever possible, the language herein must also be accurate and unambiguous in its plain meaning. At the center of this statement is the pre-implantation human embryo ("human embryo"). As used in this statement, human embryo refers to an embryo at a stage of development beginning with division of the zygote into two cells and ending just prior to implantation into a uterus (3). Such an embryo, at its most advanced state of development, is microscopic and consists of approximately one hundred cells. This definition identifies and narrows the biological entity that is the focus of the Task Force's inquiry, but more discussion is needed to illuminate the human embryo's status as an integral element in medical and scientific research. This inquiry is relational in nature as it invokes consideration of the status of the embryo in relation to the processes and goals of research. Accordingly, this position statement addresses ethical issues raised by medical and scientific research utilizing human embryos.

As a preliminary matter, it is essential to consider the status of the embryo that is used in research. In numerous contexts, the moral, legal, and ethical acceptability of an act or omission is conditioned upon the status of the entity upon which the act or omission is directed. The assignment of status positions to the entity relative to other similar and dissimilar entities permits a contextualized basis for assessing the acceptability of conduct toward that entity. Unquestionably, these precepts apply to medical and scientific research involving human embryos. The Task Force's assessment of the embryo's status borrows from decades of broad-based and thoughtful analysis of this issue. We are grateful to be guided by existing permutations of embryo status as a basis for our further consideration of the ethics of research involving human embryos.

Early framing of the status of preimplantation embryos recognized three distinct positions that could guide moral and legal outcomes. Beginning in the 1970s, national advisory boards and presidential commissions have weighed in on the question of embryo status, joined in the early 1990s by courts adjudicating the disposition of disputed embryos upon divorce (4). In general, a consensus has emerged shaping the debate around the three positions. These three positions include an understanding of the embryo as a human person, as human tissue akin to property, or as an entity that lies somewhere between person and property. This Task Force, and the American Society for Reproductive Medicine, endorses the position of "embryo as potential," wherein the embryo is neither person nor property. The positions can be described as follows:

> **Embryo as person:** This position defines the preimplantation embryo as a human person from the moment of fertilization and posits that it should be accorded the full rights of an existing person. This position asserts that the embryo has an interest in not being harmed and a right to continue its natural course of development. This position deems it morally wrong to discard embryos that have the potential to develop further, and opposes virtually any research involving human embryos. At law, this position would include embryos as persons under prevailing legal regimes, permitting civil and criminal penalties to attach upon violation of the embryo's rights.
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> **Embryo as property:** This position defines the preimplantation embryo as a category of human tissue with no independent right to continued existence. This position asserts that the embryo has no protected interests or rights akin to those of a person. Instead, the embryo is regarded as a type of property and subject to human manipulation normally permitted on other human tissue. Moral and legal principles require a certain duty of care toward living tissue but would not prohibit its discard or any research conducted according to standards governing ethics in the research setting.
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> **Embryo as potential:** This position defines the preimplantation embryo as occupying an intermediate position between a human person and human tissue. Accordingly, it is entitled to special consideration because of its potential to become a person and its symbolic meaning in the landscape of human development. The moral and legal parameters surrounding the concept of special consideration are less well-defined than in the person/property designation, and thus require principled guidance to avoid ad hoc decision-making in the research arena. Using embryos in a research setting in which the gamete providers or those with authority over the embryos' disposition have accorded their full informed consent, embryo research is ethically acceptable as a means of obtaining new knowledge that may benefit human health, well-being, or reproduction Embryos should be handled in a respectful manner in accordance with the requirement for special consideration of embryos.

Underlying each of the above positions is the biological fact that an unimplanted embryo is a genetically endowed entity that, depending on other developmental characteristics and decisions that are made, might or might not ultimately result in a pregnancy and a live born child. It is this concept of potentiality that drives the range of viewpoints on the acceptable treatment of embryos in the research setting. The position Embryo as Person regards an embryo's potential to

achieve personhood status as having been accomplished at fertilization. As a rights-bearing entity, an embryo would be entitled to the protections of equal status and vulnerability accorded human subjects after birth. While some research might be deemed acceptable, it would be limited by the embryo's inability to give consent and need for protection. Regulations surrounding research on newborn infants might be instructive, though adjustments would be appropriate to accommodate an embryo's extreme level of nascency.

The position Embryo as Property assumes that the embryo's transition from a few undifferentiated cells without consciousness, sentience or the ability to interact with others or its environment cannot be achieved without the will and skill of a trained human agent and the beneficial caprice of nature. Because an embryo has no independent ability to reach the ultimate stage of a rights-bearing person, it cannot be regarded as such a priori. Research that complies with regulatory parameters surrounding manipulation of other living tissue would be permissible, and would include consent from the progenitors, assurances (or lack thereof) of de-identification, representations about the allocation of downstream rights, and other researcher-subject exchanges that typify contemporary laboratory settings.

The intermediate view advanced in position Embryo as Potential regarding embryos as deserving of special consideration deems research as permissive under a balancing approach. If embryos are contributed by fertility patients who no longer desire that they be maintained for their own reproductive purposes or transferred to others, the decision has been made that any potential for further development has been eliminated. Similarly, embryos produced expressly for research have no reproductive destiny. They are produced with the express intent that they will not be used for reproductive purposes. Without reproductive potential, the embryo's potential for benefit shifts to the research arena, where ongoing studies in regenerative medicine, infertility treatment, genetic repair, and other health-improving advances are underway. Using embryos in medical research at the request of the gamete providers can be viewed as an exercise in special consideration because it honors the autonomy of the gamete providers by allowing them to choose to allow an embryo not destined for personhood to contribute to the betterment of human health and offspring well-being.

Importantly, a caveat is warranted to expound upon the distinction between embryos used for research and those desired for reproduction amid a rapidly advancing scientific backdrop. The position Embryo as Potential addresses the scenarios in which embryos are donated or produced for research purposes only, meaning they will be discarded or cryopreserved indefinitely. It is to this end (and concerns about embryo loss) the position is directed. Alternatively, when embryos are produced and subject to research or experimental techniques for the purpose of reproduction, their status is the same as that of all IVF embryos produced with the hope they will yield healthy, live-born offspring. The question of whether it is ethical to initiate reproduction via uterine transfer with embryos arising from novel experimental techniques is discussed herein as a matter separate from the designation of embryo status in the research setting.

This Task Force acknowledges and endorses the position previously advanced by the ASRM Ethics Committee that the embryo be regarded as worthy of special consideration. In its 2013 Committee Opinion, "Donating Embryos for Human Embryonic Stem Cell (hESC) Research," the Ethics Committee deemed embryo research as ethically acceptable "if it is likely to provide significant new knowledge that may benefit human health and if it is conducted in ways that accord the embryo respect" (5). The concept of special consideration in the research context was further illuminated by the Ethics Committee as a set of requirements that must accompany any research using human embryos. This position statement is intended to update the requirements surrounding embryo research and thus will replace the previous document in proposing an ethical approach to human embryo research.

Importantly, the Task Force concurs with the Ethics Committee that research using human embryos is ethically permissible under certain circumstances. The range of circumstances surrounding research using human embryos grows more complex each day and will require ongoing evaluation. This position statement tackles the set of research and clinical scenarios that the Task Force believes currently require assessment, mindful that goals of comprehensiveness and clairvoyance may prove illusive. It attempts to delineate an ethical framework that can be applied to the evaluation of future embryo research using techniques and approaches that have yet to become available or imagined.

II. ETHICAL CONSIDERATIONS IN EMBRYO RESEARCH

This section summarizes the important ethical considerations relevant to embryo research. At the outset, a distinction must be drawn between research that has, and research that does not have, the possibility of resulting in the birth of a child. When research has the potential for the birth of a child, its permissibility rests on the best interests of the future child. As with fetuses or children as human subjects, therapeutic research on embryos is permissible when the benefits of the research outweigh its risks. Non-therapeutic research on embryos, on the other hand, is only permissible when the risks involved are either minimal or a minor increase over minimal risk and the research offers the possibility of generalizable knowledge about the child's condition. This framework for non-therapeutic research involving children is embedded in federal regulations governing research. Non-therapeutic research with reproductive possibility would need to meet this standard for any intervention that may result in the birth of a child.

When research does not have the possibility of resulting in a future child, ethical considerations include respect for the embryo and gamete donors, special consideration of the embryo, social benefit, and justice. The Task Force believes that embryo research not intended for reproduction is ethically justifiable when it has the potential to benefit human health or well-being in the future. As with other research, embryo research must also take considerations of justice into account, such as whether the results have the potential

to benefit some social groups and disadvantage others disproportionately.

As outlined above, the Task Force endorses the view that an embryo, because of its potential to become a person, holds symbolic meaning in the landscape of human development. As such, investigators should justify the social importance of embryo research within a context that provides the reasonable possibility that the research will result in clinical benefit. Ideally, embryo research should occur when no satisfactory alternatives exist. The number of embryos produced or utilized in the research should not exceed the amount needed to answer the research question. Embryos should not be treated as commodities.

Patients who participate in the process of producing embryos may have a wide range of views about the status of the embryos that result. They may have strong feelings about the embryos they have participated in forming and they may have ethical views about permissible research that should not be violated. Respect for the donors thus requires that they give informed consent to the possibility that the embryos they donate may be used in research. As embryos embody the potential extension of their progenitors' lineage, utmost fidelity to the prospective donors' prior expressions of intent must be observed as to the use or non-use of embryos in the research setting.

III. THE CURRENT LEGAL LANDSCAPE SURROUNDING EMBRYO RESEARCH IN THE UNITED STATES

The law surrounding research using human embryos can be roughly divided into two realms. First, federal and state law address (or are silent on) the permissibility of conducting research using human embryos. These regulatory laws permit, restrict or prohibit the formation, manipulation or destruction of embryos in the research setting. Second, legal regimes address the availability of government funding for research using human embryos. In the United States, which operates under principles of federalism, individual states may express their policy preferences by, for example, banning embryo research and its funding even if the federal government permits both activities. What follows is a brief review of U.S. federal and state law regarding embryo research.

a. Federal Law on Research Activities Involving Human Embryos

No federal law expressly prohibits research activities involving human embryos; prohibitory regulations may come into play under certain circumstances when embryos are transferred into the body for reproductive purposes. Under current federal regulations, embryos that have been genetically altered cannot be used in clinical application, i.e., transferred into a human subject or patient, unless the Food and Drug Administration (FDA) has issued an Investigational New Drug (IND) exemption for the stated purpose. Since 2015, the FDA has been barred from reviewing IND applications that involve germline gene alteration in embryos, thus making any such reproductive usage illegal under federal law (6). Research that does not involve embryo transfer but rather the formation, investigation, or destruction of human embryos conducted in a manner that is unrelated to the provision of federal funding can proceed unfettered by federal law. Thus, private-sector or state-funded embryo research is permissible under federal law so long as the activity does not fall under the reach of regulation governing activities supported by federal funding. As a practical matter, determining whether a private-sector or state-funded embryo research activity has the potential to violate federal laws governing funded research can present challenges.

In 2004, The President's Council on Bioethics (PCB) briefly addressed this issue in their commissioned report on stem cell research. At that time, as today, federal law did not prohibit research using human embryos but did regulate the activity conducted using federal funds. As to non-federally funded research, the PCB clarified that, "researchers remain free to pursue work (including the derivation of new lines of embryonic stem cells) in the private sector, without government funding. Under present law, work supported by private funds can proceed without restriction. Under rules promulgated in the spring of 2002, such work does not need to be conducted in a separate laboratory, but a clear separation of the funds used to support this work from any federally funded work of the laboratory is required. Of course, because of the highly interlocking and complex nature of the various aspects of operating a laboratory, such separation can still prove extremely difficult to manage." (7). Researchers who enjoy the exclusive support of non-federal funding sources, and thus, are not subject to federal regulation specifically aimed at embryo research, are advised to seek guidance and counsel from their funders and supporting institutions as to any ancillary obligations they might have under federal law. While the nature of the embryo research can proceed unfettered, other activities in the research setting might fall under federal regulatory authority. For further information regarding federal regulations of embryo research in the United States, please refer to Appendix A.

b. Federal Law on Funding of Research Activities Involving Human Embryos

The legal and political discussions and activities regarding federal funding of human embryo research are longstanding and complex, dating back nearly half a century to the introduction of IVF and invoking the names of a half dozen U.S. presidents whose administrations weighed in on the contested issue. For purposes of this position paper, we briefly set out the current legal regime governing the provision of federal funding for research involving human embryos. A fuller account of the history of U.S. embryonic stem cell funding policy is set out in Appendix A.

The most comprehensive federal law governing federal funding for embryo research is the Dickey-Wicker Amendment, first enacted in 1995. The Dickey-Wicker Amendment is an amendment attached to the appropriations bills for the Departments of Health and Human Services, Labor, and Education each year since 1996; it restricts the use of federal

funds for creating, destroying, or knowingly injuring human embryos. It provides in relevant part:

> EC. 509. (a) None of the funds made available in this Act may be used for–
>
> (1) the creation of a human embryo or embryos for research purposes; or
>
> (2) research in which a human embryo or embryos are destroyed, discarded, or knowingly subjected to risk of injury or death greater than that allowed for research on fetuses in utero under 45 CFR 46.204(b) and section 498(b) of the Public Health Service Act (42 U.S.C. 289g(b)).
>
> (b) For purposes of this section, the term 'human embryo or embryos' includes any organism, not protected as a human subject under 45 CFR 46 as of the date of the enactment of this Act, that is derived by fertilization, parthenogenesis, cloning, or any other means from one or more human gametes or human diploid cells.

The Dickey-Wicker Amendment remains in place as an enacted obstacle to the funding of certain research activities involving human embryos. In addition to this legislative barrier, federal funding for embryo research is also subject to orders and pronouncements at the executive level. To date, these executive branch activities have touched on at least two types of research involving human embryos – human embryonic stem cell research and germline gene editing of human gametes and embryos. In the stem cell arena, President George W. Bush issued a policy statement in August 2001 limiting the provision of federal funds for human embryonic stem cell to research cell lines in existence as of the date of the statement (8). President Obama revoked that policy with his own executive order issued shortly after he took office in 2009. Under the Obama order, the National Institutes of Health are permitted to support and conduct "human stem cell research, including human embryonic stem cell research, to the extent permitted by law" (9). Detailed guidelines for funding research on stem cells derived from human embryos were issued in July 2009 and remain in effect today (10).

Advances in reproductive medicine involving genome manipulation continue to evolve and hold promise. Federal funding for protocols involving gene editing or germ line alteration in gametes or embryos is currently prohibited. In a 2015 statement, the Director of the National Institutes of Health announced that "NIH will not fund any use of gene-editing technologies in human embryos." The Director explained that "[a]dvances in technology have given us an elegant new way of carrying out genome editing, but the strong arguments against engaging in this activity remain. These include the serious and unquantifiable safety issues, ethical issues presented by altering the germline in a way that affects the next generation without their consent, and a current lack of compelling medical applications justifying the use of CRISPR/Cas9 in embryos" (11). In November 2018, the NIH reiterated its opposition to the use of gene-editing technologies in human embryos amid claims by a Chinese scientist that he edited the embryos of twin girls to assure their resistance to HIV infection (12). In addition to the generalized funding prohibition issued by the primary federal funder, a federal law enacted in 2015 prohibits the Food and Drug Administration from reviewing requests for investigational new drugs or biological products that involve "research in which a human embryo is intentionally created or modified to include a heritable genetic modification" (6). Under the law, any submission to the FDA involving genetic modification on an embryo will be deemed to have not been received by the federal agency.

c. Summary of State Laws on Research Activities Involving Human Embryos

The absence of a national law on embryo research has inevitably shifted public policy debate over this activity to the so-called "laboratory of the states." With embryo research presumptively lawful under federal law, states are free to enact their own regulatory schemes to permit, restrict, or prohibit such activity within their boundaries. State laws address a variety of research activities involving embryos, including the derivation and use of human embryonic stem cells, experimentation involving embryos and fetuses, the purchase and sale of human tissue for research, the use of somatic cell nuclear transfer, and the parameters surrounding informed consent and institutional review processes for research involving human gametes or embryos. The National Conference of State Legislatures (NCSL) maintains a listing of all state laws governing research involving embryos and fetuses (13). According to NCSL, as of January 2016, there are 8 states whose laws permit research on human embryos (California, Connecticut, Illinois, Iowa, Maryland, Massachusetts, New Jersey, and New York) while 24 states have laws that prohibit some aspect of embryo or fetal research (Arizona, Arkansas, Florida, Kentucky, Louisiana, Maine, Michigan, Minnesota, Montana, Nebraska, New Hampshire, New Mexico, North Dakota, Ohio, Oklahoma, Pennsylvania, Rhode Island, South Dakota, Tennessee, Texas, Utah, Virginia, and Wyoming). Restrictions in these latter states vary considerably, making consultation with a qualified expert in the field essential.

d. A Summary of State Law on Funding of Research Activities Involving Human Embryos

State activity on the use of public funds for research involving embryos has created opportunity for support in a limited number of jurisdictions. According to the National Conference of State Legislatures, a handful of states (fewer than 10) has taken a position of the use of public funds for embryo research, with several states (Missouri, Maryland, Arizona, Nebraska) either prohibiting or restricting expenditures for embryonic stem cell research. In some cases, public funds may be used for therapeutic research but not for techniques that involve human cloning. The most prominent state funder of embryonic stem cell research is California, based on a ballot measure approved by voters in 2004. Proposition 71 created by the California Institute for Regenerative Medicine which is charged with making "grants and loans for stem cell research, for research facilities and for other vital research opportunities to realize therapies" (14). Other states that fund

aspects of embryonic stem cell research include Connecticut, Maryland, New Jersey, and New York (15) .

IV. CONSIDERATIONS FOR CONDUCTING RESEARCH USING EMBRYOS

Embryo research can be broadly divided into two categories aligned according to whether it has reproductive intent. Reproductive intent is determined according to the planned disposition of the embryos at the time the research commences and throughout its duration. Research in which the embryos will not be made available for pregnancy and childbirth at any time is research that lacks reproductive intent. Research in which the embryos may be made available for pregnancy and childbirth in the course of the research or any time thereafter is research that has reproductive intent. In research devoid of reproductive intent, embryos are never transferred into the uterus (or if clinically possible in the future, maintained ex-utero until the developing fetus can survive independent of the supporting mechanisms). Examples of such research include the use of CRISPR technology to perform gene editing and study the efficacy and safety of such technology prior to its application in treating genetic diseases in human embryos (16, 17). When research lacking reproductive intent leads to the development of embryonic stem cell lines, these cells may be kept in the laboratory and studied indefinitely. In contrast, research with reproductive intent has pregnancy and live birth as a goal.

Research with reproductive intent necessitates a more exhaustive process to understand the potential for and extent of untoward outcomes prior to attempting to use embryos for reproduction. These outcomes include ones posed to the resulting offspring, and those that may be passed on to future progeny. Embryo research that is conducted with the goal of transfer into the uterus, pregnancy and childbirth should only be undertaken after pre-clinical research demonstrates acceptable levels of safety and efficacy. Embryo research with the intent of achieving a viable pregnancy should only be undertaken with the intent of improving health or well-being or allowing for reproduction when no other reasonable or feasible alternatives exist, or the innovation offers significant benefit over existing options. Special attention needs to be given to research that may affect the genetic or somatic make-up of future generations to ascertain that the intended goals of research are met and that unintended sequelae do not occur. Given the nature of reproduction, it must be recognized that such sequelae may not be known for decades or generations. As such, any such research must delineate a procedure for reporting on the health and well-being of both first generation and subsequent offspring, to ensure that any potential negative effects to those born following clinical interventions are identified in a timely manner and not perpetuated indefinitely.

a. Justification for Research Using Human Embryos

Many important scientific questions regarding human reproduction, development, fertility and regenerative medicine can only be answered by research involving human embryos. While alternatives to research with embryos may be less ethically divisive, such research is not scientifically equivalent and the questions under investigation may not be answerable in the absence of human embryo research. Indeed, demonstrating that alternatives to embryo research are viable often necessitates the use of embryos. Certain branches of research can only be pursued using embryos. In order to establish parameters for investigating questions of human development, reproduction and fertility, it is critical that scientists and society at large work to obtain an understanding of which research questions might be answered by studying embryos and which can be elucidated through other means.

Embryos are valuable by virtue of the means of their formation, their limited availability and their potential to develop into human beings. As such, they should only be used for research to improve human health, well-being of the offspring or reproduction. Setting parameters and goals for the scope of embryo research and its potential application in reproduction should be the subject of robust scientific and ethical debate at the outset. Myriad questions abound, including whether research and clinical application should be exclusively directed toward identifying disease causing genes in early embryos in order to avoid their transfer, or whether gene-altering technologies should also be used for the eradication of disease and the promotion of health in human beings. Whenever possible, the number of embryos used for research should be minimized. Research protocols should be carefully formulated to maximize scientific output. Robust oversight mechanisms should be established to ensure that investigators rigorously adhere to the highest ethical standards.

The scientific discoveries resulting from embryo research have the potential to impact our world in very significant ways. However, knowledge gained from embryo research is one of many discoveries in the medical arena that have transformed human life and health. Examples include the development and utilization of antibiotics, which have changed not only the bacterial microbiome within humans but that of the biosphere itself, and transplant surgery which led to a questioning of human identity and bodily integrity (18, 19). Gene editing of embryos is no less profound, having the ability to alter the genome not only of the child that results but of that child's offspring in perpetuity. This requires additional long-term and carefully considered oversight over multiple generations to ensure that the changes made to one individual do not have untoward effects either to the proband or to future generations. Extensive and comprehensive research is a prerequisite for the clinical application of knowledge gained from the study and manipulation of embryos. It is critical that investigations occur under a controlled environment and with appropriate oversight.

Human embryos have a number of unique characteristics that can only be understood by investigating the embryos themselves. The current state of knowledge suggests that early embryos express a high rate of aneuploidy, some degree of mosaicism and a low rate of implantation. Understanding the role that aneuploidy and mosaicism play in human development could be vital to advances in human health and reproduction. A complex cascade of gene expression needs to occur

for the activation of the embryonic genome. Research on early stage in vitro human embryos holds the promise of improving our understanding of the molecular, cellular, genetic and epigenetic mechanisms that control the development of early human embryos. No surrogates for human embryos exist for this type of research. In addition, in order to increase the efficacy of IVF treatment by reducing implantation failure, the incidence and extent of aneuploidy and mosaicism would benefit from further study.

A major focus of embryo research is the avoidance of disease. The earliest form of this research involved sexing embryos and only transferring females to avoid transmission of X-linked disorders. Preimplantation genetic testing has evolved since these early days. It is now possible to screen embryos for any disease or predisposition whose genetics are known, thereby allowing for the transfer of unaffected embryos. This is effective so long as at least one of the screened embryos is unaffected by the disease or predisposition which the screening attempts to prevent. As the safety of preimplantation genetic testing has become established, its use has evolved from testing only for diseases that have severe disability or early death as their sequelae to milder diseases and disease predispositions. This model, of starting with the more severe cases, serves as a good example for the carefully considered incorporation of embryo research over time.

Preimplantation genetic testing as a strategy to avoid disease in offspring and optimize reproductive success has several limitations. Some couples will only produce a limited number of embryos, all of which will be affected by the disease of interest. In other rare cases, such as mitochondrial disorders, all embryos may lead to affected offspring. Avoiding disease transmission in such situations requires incorporation of unaffected mitochondria. Chromosome spindle transfer into enucleated donor eggs was the first modality used to attempt repair of such a diseased embryo (20). One of the most profound embryo altering technologies to date is that of germline editing using methodologies such as the CRISPR/Cas 9 system (21), which could allow for correction of genetic errors in the DNA of an early embryo. The intrauterine transfer of such an embryo would have as its goal the birth of a healthy child, with removal or correction of the disease-causing mutation(s). Because the genetic modification would occur in every cell of the embryo, including germ cells, such heritable alterations raise questions regarding the risks of permanent genetic modification. Given this, such research should initially focus on genes for which strong evidence exists for a link between the gene and the resulting disease or disease predisposition.

Furthermore, early research should be restricted to genetic alterations that prevent serious diseases with significant health effects for which effective medical treatment or other preventative measures are currently absent, limited or highly burdensome. Extensive research that does not have reproductive intent should be carried out before any transfer of gene altered embryos to the uterus for the purpose of achieving a pregnancy is attempted. Careful consideration should be given to the risks versus benefits of gene altering technologies as compared to preimplantation genetic testing, in which no genetic manipulation is undertaken. Such consideration should include the potential risks of unintended sequelae to future generations from the use of germline editing technologies. On the other hand, the possibility that more embryos would be available for reproduction after in vitro fertilization if some embryos could successfully undergo genetic repair should also be part of the calculus.

In addition to avoiding disease, the direct study of poor-progressing or aneuploid human embryos can lead to further understanding of specific mechanisms of cell differentiation and early development. Research on the trophectoderm can be used to delineate mechanisms which allow for or inhibit implantation thereby improving reproductive efficacy. Stem cell lines derived from embryos have allowed for a better understanding of normal and abnormal cell development. The pluripotency of embryonic stem cells provides insight into cellular mechanisms that lead to cell differentiation, and provide a window for the study of regenerative medicine. Stem cells provide a renewable source of cells and tissues whose study holds promise for the development of novel cures and treatments for a range of human diseases.

Over the past several decades, research on supernumerary embryos following IVF has led to a growing understanding of the cascade of events necessary for successful in vitro development and uterine implantation. Such research has resulted in dramatically improved clinical outcomes with in vitro fertilization and a rise in the number of live births following fertility treatment. It has helped prevent the birth of children with severe diseases, and decreased the burden of spontaneous abortions and failed implantation. It is estimated that there are currently over one million embryos cryopreserved in the United States, with more being added each year (22). The proliferation of supernumerary embryos is a byproduct of the fact that fertility treatments are not an exact science, such that in some cases more embryos are produced than are necessary to complete a given individual or couple's family plan. Infertility patients are often burdened with the necessity of determining the disposition of these embryos. The possibility of contributing to further advancement of the scientific understanding of human development and fertility is felt by many previously infertile individuals and couples as the best possible use of the embryos that were originally produced with reproductive intent. Even a small percentage of donated embryos translate into a significant number of embryos available for research. Many of these embryos would otherwise have remained cryopreserved indefinitely or been discarded.

b. Alternatives to Research Using Human Embryos

It is a tenet in the research arena that knowledge should be gained while minimizing unwanted negative effects. In some cases, knowledge regarding processes which improve human reproduction, health or well-being may be obtained via modalities that do not involve the study of human embryos. These include the use of animal models, the use of stem cells from the umbilical cord or adult tissue, the derivation and study of induced pluripotent stem cells h(IPSC), the activation of human oocytes by parthenogenesis, and the development and study of synthetic embryos. These

alternative methods to the use of human embryos may have the potential to yield valuable insights and outcomes, but their limitations need also be considered.

Animal models (i.e. utilizing non-human primate embryos or other animal embryos) offer an excellent opportunity to understand some aspects of human biology, and have been widely adopted. Further, use of transgenic or genetically manipulated animals offers the opportunity to influence the developmental trajectory and to test a hypothesis. However, findings in animals may not be relevant to humans as unique developmental pathways may be peculiar to each species (23). Stem cells isolated from umbilical cord blood have been shown to have some ability to differentiate into non-hematopoietic cells, such as brain, heart, and liver (24). However umbilical stem cells and stem cells derived from adult tissues have already progressed along the path of differentiation and lack the plasticity of embryonic stem cells. This lack of plasticity limits their usefulness in reproductive research. Unfertilized human oocytes can be activated by parthenogenesis and can recapitulate some early stages of embryo development. However, the absence of the paternal genome and the lack of expression of the related imprinted genes are serious limitations of this strategy.

The advent of induced pluripotent stem cells (iPSC), by utilizing adult somatic cells that have been reprogrammed to an embryonic state in response to the introduction of transcriptions factors is being developed as a new research modality, allowing for the de-differentiation of adult cells to an earlier developmental state (25) . iPSC behave like embryonic stem cells in many respects, and have the ability to differentiate into all germ layers. Furthermore, these cells can be used to study complex human diseases, such as Alzheimer's and cardiac diseases (26, 27). This method would seem to bypass the ethical quandary of having to utilize an unimplanted embryo. However, iPSC appear to maintain an epigenetic memory of their original state with a predisposition for differentiation into their cell of origin (28); thus limiting their ability to exactly mimic the early stages of embryo development (29).

A currently emerging new technology, called "synthetic embryology", allows generation of what has been defined as "synthetic human entities with embryo-like features," or SHEEFS (30). Human embryonic stem cells grown on a scaffold of soft gel tend to rearrange themselves into embryoid bodies. These bodies can recapitulate lumen formation and the polarization of the early epiblast in a way that is similar to the early stages of pro-amnionic cavity development in actual embryos; furthermore, these colonies can develop features identifiable as a primitive streak with cells from all three germ layers (31).

Human embryonic stem cells (hESC) are highly valuable for the richness of information that can be elucidated from their study. These stem cells are derived from unimplanted human embryos. One or more cells of human embryos are obtained either via biopsy of an embryo that will be utilized for transfer, or by removing one or more cells from an embryo that is either not viable or not destined for transfer. The utilization of hESCs is a viable option in the United States, but has substantial limitations. Federal law contained in the Dickey-Wicker Amendment prohibits federal funding to generate new embryonic stem cell lines if derivation of those lines results in the destruction of the embryo. In addition, some existing embryonic stem cell lines available for research on the National Institutes of Health (NIH) registry were cultured in contact with mouse cells and bovine serum, a fact that greatly limits their potential therapeutic applications.

Research on human embryos should be allowable when alternative means to gaining knowledge prove inadequate. The Task Force recognizes that while alternative methods might be excellent for selected inquiries, they do not comprehensively capture the complexity and uniqueness of human embryos. There are circumstances where human embryos need to be studied because this will be the only opportunity to gain meaningful and applicable data. Furthermore, applying knowledge gained from modalities other than human embryos may lead to harm by not providing adequate insight into the unique functioning of human embryos. In all cases, research on human embryos not intended for reproduction should be a precursor to research involving the transfer of embryos that have been altered in an attempt to improve their reproductive efficacy or the health and well-being of the resultant offspring.

V. ETHICAL CONSIDERATIONS IN GERMLINE GENE EDITING

Germline gene editing involves the alteration of genes within germ cells (oocyte and sperm) or embryos and results in changes that are theoretically present in all cells of the embryo (32). Germline gene-editing research can use gametes, viable or non-viable embryos remaining from IVF, or embryos produced specifically for research. Germline gene editing is particularly controversial because changes made in the germline could be passed down to future generations. The main ethical concerns relate to safety and efficacy, informed consent, and justice and equity.

Safety concerns with germline gene editing include so-called "off-target effects" (when edits are made in the wrong place in the genome) and mosaicism (when some cells are edited and others are not). Because of these risks, most researchers agree that until germline gene editing is deemed safe, it should not be attempted for reproductive purposes until studies without intent to transfer these embryos into the uterus establish safety and efficacy. Specific safety concerns include the effect of unwanted or off-target mutations potentially resulting in inactivation of essential genes, activation of oncogenes, or rearrangement of chromosomes. Various methods are being explored for the monitoring of off-target effects. There is currently no consensus on which method is optimal or what is an acceptable level of off-target mutations. This is even more challenging because the biological material is usually limited. Furthermore, the relative health risk of off-target mutations is often unclear. The specificity of gene editing must be evaluated in the context of the normal genetic variability among humans. New methods will need to be developed for identifying and monitoring off-target effects in the embryo and in-vivo.

Additionally, gene editing may carry the risk of genetic mosaicism, if it is unable to affect all cells uniformly. Safety

concerns should be investigated with further research using animal models ideally followed for multiple generations. Long-term animal research may not be able to provide guidance in a reasonable time frame. Work in non-human primates is slow, expensive, and limited to centers with primate colony resources. Moving this research to the clinic requires the determination of a favorable risk-benefit ratio. Human clinical trials should follow children into adulthood, with the consent of all parties involved.

Questions about efficacy in germline gene editing also loom large. What impact will gene deletion or addition have on the overall health of the offspring? How will gene editing in the embryo impact the expression or suppression of diseases not specifically targeted by the editing? Will the elimination of one genetically-based disease give rise to the expression or susceptibility of other diseases? These and other critical questions need to be addressed before any clinical applications can proceed. In the meanwhile, the use of germline gene-editing not intended for reproductive purposes should be directed towards studying these and other questions while focusing on eliminating or preventing diseases with significant impacts on the health or well-being of offspring.

While alternative methods for disease prevention in ART such as preimplantation genetic testing (PGT) exist, PGT is not applicable in all circumstances. For example, in rare cases when both prospective parents are homozygous for a recessive disease-causing mutation or one prospective parent is homozygous for a dominant disease-causing mutation, all resulting embryos would be affected with the disease. Furthermore, if proven safe and effective, germline gene editing may improve the efficiency of PGT by increasing the number of embryos available for transfer and reducing the burden of IVF, including the associated physical risks and costs. Also, for some patients PGT may pose moral or ethical dilemmas surrounding disposition when one or more, or all embryos are determined to contain a disease-causing mutation. For patients who desire a healthy child but who disfavor embryo discard or cryopreservation, the use of PGT could yield disease-affected embryos whose ultimate disposition could pose moral or ethical distress. Theoretically, gene editing technologies could relieve this moral distress by limiting the embryos produced to those that are disease-free.

Another concern is that germline gene editing for therapeutic uses may lead to a "slippery slope" to using it for indications beyond disease avoidance and promotion of well-being of the offspring. This is often referred to as enhancement. Many view the use of reproductive technologies to alter that which is "normal" in the human condition to gain some perceived advantage as controversial. Others argue that these concerns can be managed through policy and regulation. Still others argue that parental desire to enhance the health and well-being of their children is an existing, long standing and laudatory aspect of parenthood that is operationalized in numerous ways beginning with prenatal caretaking and continuing throughout the child's life cycle. That said, there is concern that perceived enhancement technologies, once available, will be used for objectionable purposes in parts of the world with less robust regulations and oversight. As with many reproductive technologies, the possibility that germline gene editing will only be accessible to the wealthy and will increase health stratification among socioeconomic classes and disparities in access to healthcare raises concerns regarding a lack of distributive justice.

Some people argue that patients ultimately affected by these edits, the children and future generations, cannot give informed consent. Yet, prospective parents make many decisions that affect their future children who do not give informed consent. In fact, the very act of human conception produces a person with a unique genome, aspects of which can persist in future generations, and no consent is sought or received from the would-be child. In the context of embryo research using gene editing, there is concern about being able to obtain fully informed consent from prospective parents when the risks of germline gene therapy are largely unknown, and the technical complexities surrounding the processes are massive. In order to fully assess the risks, there is a need for long-term follow up of the resulting children.

The National Academies of Sciences recently concluded that germline gene editing for the prevention of serious genetic diseases is ethically acceptable, but that it should not be used for enhancement purposes (33). The NAS also concluded that germline gene editing should not be attempted for reproductive purposes at this time because of the lack of safety and efficacy data (34). While supporting the continuation of pre-clinical research, the NAS concluded that "clinical trials might be permitted after peer-reviewed preclinical research further clarifies the potential risks and benefits, only for compelling medical reasons in the absence of reasonable alternatives, and with maximum transparency and strict oversight" (33). Similarly, the UK-based Nuffield Council on Bioethics concluded that germline gene-editing is ethically acceptable as long as it secures the welfare of future children and does not increase disadvantage, discrimination, or division in society (35). In 2015, a group of leading scientists and ethicists at the forefront of reproductive research published a consensus statement delineating a cautious approach to genomic engineering and germline gene modification (36). Following the announcement at the second international summit on gene editing in Hong Kong in 2018, the presidents of the U.S. National Academies of Medicine and Science, and the president of the Chinese Academy of Sciences issued a call to action, stating that "To maintain the public's trust that someday genome editing will be able to treat or prevent disease, the research community needs to take steps now to demonstrate that this new tool can be applied with competence, integrity, and benevolence" (37). Both the National Academies and the Nuffield Council urge continued societal debate on the topic of germline gene editing. This position statement is aligned with that recommendation, set out as an additional voice in this ongoing conversation about a vital public policy matter.

VI. APPROACHES TO OVERSIGHT: MECHANISMS FOR APPROVAL, REVIEW, CONSENT AND REPORTING IN EMBRYO RESEARCH

a. Oversight Mechanisms

Much research involving human embryos takes place in settings such as private clinics that are not within the explicit purview of existing regulatory structures. Thus, initial questions about oversight of embryo research are whether it should be recommended at all, whether a requirement to report research is sufficient (and how such a reporting requirement should be structured and monitored), and whether facilities conducting the research should be ethically encouraged or required to employ existing regulatory structures for oversight. If oversight is to be recommended, an additional question is whether to rely on the existing regulatory framework established by the Common Rule (a multipart federal regulatory scheme governing the protection of human subjects in biomedical research first promulgated in 1981) or to develop a new oversight structure specifically for embryo research (38).

Given the complex ethical issues involved in research involving human embryos, the Task Force believes that oversight of the research process is essential. The primary oversight mechanism for research involving human subjects in the U.S. is the system of institutional review boards (IRBs) established by the federal Common Rule. As outlined below, the Task Force recommends use of the Common Rule/IRB framework for research involving embryos, even when the facility conducting the research falls outside of structures in which the framework is legally required.

The Common Rule applies to research sponsored by federal agencies subscribing to the rule; similar standards also apply to research to be submitted to the Food and Drug Administration (FDA) for marketing approval of drugs, devices, or biologics (39). The Common Rule requires IRB review and approval of research, although some reviews may be expedited and some categories of human subject research are exempt. A primary difference between the Common Rule requirements and the FDA requirements is that the latter impose more stringent expectations for informed consent. If research is not federally funded or if there are no plans to use what is learned for submission to the FDA, this regulatory structure may not be mandated. However, many larger institutions, such as academic medical centers, choose to apply both the Common Rule and the FDA requirements to all the research they conduct and make assurances that they are doing so to the federal government. Some states also have legal requirements that apply to embryo research; these requirements range from complete prohibition to efforts to encourage stem cell research (40). Clinics falling outside these structures would not be legally required to follow the Common Rule but in the judgment of the Task Force should be encouraged to do so.

The definition of "research" is important for understanding the scope of the federal Common Rule. "Research" is "a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge" (38). The variety of quality improvement activities conducted by clinics is not research under this definition, and thus would not require IRB review. However, under ASRM Ethics Committee opinions patient consent is required for the use of embryos in quality improvement efforts by clinics (41).

In the judgment of the Task Force, oversight of research involving embryos should occur in a consistent manner across all facilities that perform human embryo research. Embryo research has the potential to be ethically complex and politically controversial. Because there are differing judgments involving the status of the embryo, as discussed in the first section of this position statement, these controversies attend all embryo research, whether or not it is conducted with reproductive intent. This research can be expected to draw ongoing public concern. It is recommended that any sponsor (funder) of human embryo research establish its own guidelines for initial review and subsequent oversight of such projects. Even if such guidelines permit ceding such review and oversight functions to local or commercial institutional review boards, it is reasonable to recommend for the sponsor to have a role in the initial review of compliance with guidelines for human embryo research and again prior to the release of funds.

Furthermore, given that research embryos are scarce commodities, it is of vital importance that robust efforts be made to maximize the knowledge gained from each research project. To this end, researchers should be encouraged to publish their findings in a peer reviewed manner as soon as is feasible. Making this a prerequisite of research funding will increase the transparency of the research and allow a large swath of experts to analyze the data and advance the science in a collaborative manner. This will allow the community of researchers timely access to the knowledge gleaned from embryo research, ultimately benefiting society as a whole. Given the complex issues surrounding germline gene editing, full disclosure regarding future research should be encouraged. One mechanism for achieving such disclosure is through the development of a registry for current and future experiments in this field.

b. Application of the Common Rule to Consent for Embryo Research

Standards for informed consent to research involving embryos have been discussed in several previous ASRM Ethics Committee opinions. For example, in the case of donating embryos for human embryonic stem cell (hESC) research, the Ethics Committee recommends that donation occur only after patients' therapy is complete and only after a process of consent (5). The Committee's opinion addressing the disposition of abandoned embryos specifies that "in no circumstances" should abandoned embryos be used in research without consent on the part of patients (41). These specifications do not cover all the ethical issues involved in embryo research, however, such as minimization of embryo use or attention to the potential risks of this research especially when it has reproductive potential.

Establishing a separate framework for all embryo research instead of relying on the Common Rule structure also would be difficult, for several reasons. Embryo research bears many similarities to other research involving human tissues; establishment of a separate framework for this research is potentially reduplicative of efforts already in place at many institutions. Such a separate framework could be inefficient and create the possibility of inconsistencies in reviewing research. Moreover, the IRB framework is well known and readily available, even for entities in the private sector. Finally, use of this framework creates a common practice for all embryo research.

At the same time, care must be taken in the application of the Common Rule framework to human embryo research. This framework may be undergoing significant changes over the next few years. A final rule for revisions to the Common Rule was published on January 19, 2017, to become effective one year later; implementation of these revisions was delayed until January 2019, when the updated provisions took effect. The current Common Rule does not apply to tissue samples that have been de-identified (42) and this provision is continued in the revised Rule (43). Although some patient advocates argued that it was important for them to be aware of and consent to the use of tissues that had been derived from their bodies, others commenting on the Common Rule revisions were concerned that a requirement of consent for all use of human bio-specimens, whether or not they were identified with individuals, would significantly constrain the research enterprise. This concern about impact on research prevailed in the final rule (44), which does not require consent to research involving tissues that do not contain information identifying individuals.

The revisions to the Common Rule offer an additional possibility regarding consent to research with identified tissue samples - "broad consent." This mechanism may give clinics an important new option to enable non-reproductive research involving embryos that can be identified. Under the broad consent mechanism, individuals could consent to any subsequent research use of identifiable tissue samples. At this point, the distinction between non-reproductive research and research in which reproduction is intended is critical. In the judgment of the Task Force, it is permissible for patients to consent in advance to any form of embryo research that does not lead to reproduction, including future research that is as yet unidentified or unknown at the time that the embryos are donated. Contemporaneous consent for research, that is, consent obtained at or just prior to the commencement of research, is not intended to result in reproduction should not be required. Consent for research at an earlier time, including at the time embryos are produced or subsequently when a decision to donate supernumerary embryos is made, is sufficient.

This is not the case for research with reproductive intent. Given that embryos have reproductive potential, and that individuals should never be compelled to reproduce without their knowledge or without their consent, any embryo research with reproductive intent should only occur with the explicit consent of the individuals who have dispositional authority over the embryos (this may be the gametes providers or, in the case of gamete donation, the gamete recipients/intended parents). This consent should occur at the time that the embryos are donated for the specific research project; broad consent in anticipation of the possibility of research with embryos that are no longer needed for fertility treatment is inappropriate for embryo research that has reproductive potential and requires a new consent from those individuals responsible for the initial generation of such embryos or those with decisional authority over the embryos' disposition.

VII. SOURCES OF EMBRYOS FOR RESEARCH AND THE ROLE OF HUMAN SUBJECTS: COMPENSATION, CONSENT AND CONFIDENTIALITY IN EMBRYO RESEARCH

Embryos for research may arise from multiple sources. A common source is from the donation of supernumerary embryos that result from in vitro fertilization procedures in excess of what is needed to complete the individual or couple's family plan. The use of donated supernumerary embryos for research raises questions about any compensation paid to gamete providers or those donating the embryos for research, as well as issues surrounding the consent process once a decision has been made to donate.

a. The Question of Compensation for Embryo Donation

The Task Force reviewed a number of positions regarding payment for embryos to be used in research protocols. The vast majority of published statements on this question hold that individuals donating embryos that were originally produced with reproductive intent should not be paid as an enticement to make their embryos available for scientific investigation (45, 46). The Task Force supports this view while acknowledging that individuals may reach different conclusions on the subject and that practices in research arenas across the country may vary, including offering reimbursement of storage fees incurred by donors who later agree to provide embryos for research purposes. The Task Force recognizes that individuals will need to come to their own respective decisions in this area. Further, the Task Force believes that the formation of human embryos expressly for research purposes is ethically acceptable so long as the proposed research is consistent with the ethical recommendations set out in this position statement. Payment to egg and sperm donors who produce gametes solely for research purposes is ethically acceptable in the same manner as other human subject research participants are compensated for such participation. While understanding that decisions in this area are for individual judgment, the Task Force believes it is useful to express its considered judgment on this subject.

The Task Force believes that the decision to donate embryos initially produced with reproductive intent should be delinked from the enticement of donors to surrender embryos for reasons other than pure donative intent and/or a desire to support scientific advancement. The time, effort and cost to produce these supernumerary embryos were expended with reproductive intent, and the Task Force does not believe

that subsequent compensation for their donation can be ethically justified. Embryos may also be produced specifically for research, in which case the potential for reproduction was never the impetus for their formation. This can occur when research involves a specific disease, and gametes from individuals who express or carry the disease of interest are sought out. In such cases, the formation of disease-specific embryos may be the best method to advance the understanding and treatment of the underlying disease. Embryo formation for research purposes can also occur if there is a shortage of embryos. Financial compensation of men and women who provide sperm and oocytes for reproductive purposes has long been accepted in the United States. Reimbursement to individuals providing gametes for research should likewise be permitted. The Task Force acknowledges the seemingly disparate treatment accorded gamete donors who often do not receive compensation in connection with their donation when its purpose is research as opposed to reproduction (47). However, it is essential to highlight that the advocacy for compensation to gamete donors, particularly oocyte donors, is for the "time, inconvenience, and discomfort associated with" the donation process.

b. Informed Consent and Confidentiality in Embryo Research

Obtaining the informed consent of those with dispositional authority over embryos donated for research purposes is an essential, indispensable process that must precede any use of embryos in a research setting. When derivation of human embryonic stem cells (hESC) from the donated embryos is the intent of the research, this information should be included in the informed consent process. Such consent should make sure that the donors are aware that the removal of the inner cell mass of an embryo for the derivation of hESCs leads to the destruction of the embryo. It should also inform the embryo donors that cell lines may be stored indefinitely, and used for multiple research projects, and be shared among more than one investigator. They may be used for basic research and/or to develop new drugs, tests, treatments or products that could have potential commercial value. As part of the consent process, embryo donors should be informed that they will not derive any direct benefit from research performed on their donated embryos. Embryo donors should be reassured that their donated embryos will not be used for reproductive purposes.

Further, if known, information regarding the specific type of research planned, the source of funding, the research's possible commercial value and potential clinical applications should be disclosed (5). Disclosure surrounding the potential commercial value of any research or its results should include any compensation or other financial benefits that might inure to one or more members of the research team (48). Broad consent is also acceptable, in which the initial consent for research embodies a large swath of potential future research uses and known commercial benefits. The embryo donors should be informed that they would not receive financial compensation from any commercial uses of technologies and therapies that are developed from research involving their donated embryos (49). It is also valuable to consider the extent to which individuals and couples considering embryo donation may stipulate which forms of research they find ethically acceptable for their donation. Many of those considering donation are appreciative of and impacted by the specificity of research plans (50). Those obtaining informed consent should be as specific as possible about current research projects for which embryo donations are intended to the extent this can be known. This allows patients to opt out of specific projects which may be ethically unacceptable to them.

The confidentiality and privacy of the embryo donors should be a priority, and all genetic samples should be de-identified to the extent possible. However, given the growing ability to match individuals with their genetic samples, donors should be aware that anonymity cannot be absolutely guaranteed into the future. There also may be cases in which additional information about the donors is necessary for the research; in such cases, privacy and confidentiality should be protected to the extent possible but donors must be informed that it cannot be guaranteed. At the same time, donors should be informed that they will not necessarily be alerted to information learned from their genetic material. Donors should be counseled that if disclosure of genetic information is provided for in the research protocol, the revelation of information gained from research on embryos may affect the donors, their family members and their offspring, and they should be given the option of not receiving such information.

In some cases, couples donating embryos for research produced these embryos with the assistance of an oocyte or sperm donor. In most cases, oocyte and sperm donors consent to relinquish all rights and interests to their donated gametes once the gametes leave their bodies. This then allows the recipients of the donor gametes to make decisions regarding the ultimate disposition of the embryos produced from donor oocytes, sperm or both. Whether such broad consent also applies to research uses that involve the derivation of stem cell lines or the alteration of the genetic makeup of an embryo has not been established. Ideally, the initial consent that occurs at the time that the gamete is donated should include all potential future uses of the embryos produced from the gamete donation. This becomes complicated when research directions that could not have been envisioned at the time of the gamete donation become a reality. Such complexity should be included in the initial consent process, and allowances should be made for the gamete donors to either opt out of specific future uses or to specify which types of research they consent to for the resultant embryos.

Another possibility is to utilize a roll-down consent method in which the oocyte or sperm donors provide broad consent for future research of embryos that remain after the gamete recipients have utilized the resulting embryos to complete their family plan. This consent would specify that the ultimate disposition of the embryos would be determined by the gamete recipients at a future date once they no longer require the resulting embryos for reproductive purposes (51). The exception would be that the recipients would not be permitted to donate the embryos for any research use that includes

reproductive intent without explicit consent from the gamete providers.

VIII. THE ROLE OF PUBLIC PERCEPTION IN DECISIONS SURROUNDING EMBRYO RESEARCH

The pursuit of embryo research and the incorporation of scientific findings resulting from this research have been affected by a number of factors. One of these is the availability of embryos, research tools and investigators which allow the scientific process to flow. As seen in a previous section, regulation has played a significant role in how embryo research is undertaken and funded. Public opinion is yet another determinant which influences embryo research. Strong sentiments in support of or against embryo research in the populace affect voting, government spending and ultimately public policy.

There have been several research polls in recent years that attempt to assess public opinion towards embryo research. One issue with polling Americans regarding their views on this controversial topic is the variability in the public's knowledge regarding this issue. In general, Americans who have more familiarity with the types of research that can be performed using embryos and the types of clinical applications that may be developed have an increased comfort level both with the pursuit of this research and its funding. However, many Americans admit to a lack of exposure to this area of investigation, thus preventing them from having views and opinions regarding such research. For example, one poll from 2016 found that 69% of Americans have heard little or nothing about germline editing (52). A Pew research poll conducted in 2018 found that 42% of those surveyed said they had not heard or read about gene editing (53). In 2015, a Hart Research Associates survey found that over a quarter of Americans surveyed online stated that they did not know enough to have an opinion either way regarding heritable DNA modification (54). This was particularly pronounced among seniors, of which 42% felt that they had not heard enough about the technology to provide an opinion (55). A Gallup poll conducted in 2005 found that of those surveyed, 58% state that they have followed the debate about government funding of stem cell research very or somewhat closely, and 42% stated that they either did not follow the debate or did not do so too closely (55). Further information regarding the results of polling in understanding the public's views towards emerging genetic technologies may be found in Appendix B.

The study of public perceptions towards embryo research highlights the urgent need to provide education to the population at large regarding the scientific underpinnings of embryo research. Such education should focus on providing knowledge to allow for an understanding of the possible research questions that may be answered by studying embryos. Armed with such knowledge, a robust dialogue may be undertaken to allow for maximal societal engagement in making funding and research decisions that will shape the future of our understanding of reproduction, health and disease.

IX. CONCLUSIONS

The study of human embryos is not new. The first report of a successful in vitro fertilization of an oocyte occurred over 50 years ago (56), and the first child born from in vitro fertilization is now over 40 years old (57). To date, over eight million babies have been born following in vitro fertilization (58). Since its earliest days, the study of embryos has engendered a fierce debate regarding morality, ethics and the public good. Then, as now, federal funding sources were often not available to support embryo research, and private funds were utilized (59). Nevertheless, embryo research and its clinical applications continue to march on. It has been over two decades since the first human embryonic stem cells were isolated, allowing for vast and varied research whose aim is the acquisition of scientific knowledge for the advancement of health and well-being. Most recently, gene editing technologies have become possible, and research aiming to change the genetic milieu of an unimplanted embryo has raised significant controversy.

Over the course of history, each novel scientific advancement led to a reevaluation of what can and what should be done. Scientific breakthroughs are often accompanied by a debate over their true sphere of influence and the magnitude of their impact. Embryo research is no exception. The ethical underpinnings inherent to embryo research are no different than those applied to any other area of scientific investigation. And yet, studying embryos feels somehow singular. Embryos, by virtue of their ability to become children, hold a special uniqueness due to their developmental potential. Changes in these embryos may be perpetuated indefinitely over future generations. Many technological breakthroughs impact generations of humans, but none are as emotionally and ethically charged as those involving embryos. Perhaps this is due to the inability to separate humans' perception of the essential nature of the embryo from the teleological question of what it means to be human.

Society is at a juncture. While the pace of scientific inquiry appears to be advancing at lightning speed, the scientific community's ability to both learn from and influence the embryo is yet in its infancy. We have the profound responsibility to guide the course of research in this field in a way that follows the ethical tenets that are inseparable from the just and responsible process of research. This is no small feat and requires collaboration of all of the stakeholders. While scientists have a role in determining what is possible, society at large should guide what should be done. Citizens should direct public policy and guide governmental and regulatory policies so as to safeguard this research and its implementation. At the heart of this is education, for without an understanding of what can be done, we will not as a society possess the tools to guide what should be done. As an understanding of both the safety and efficacy of new technologies, particularly in the realm of gene editing, evolves, the dialogue will change. We should as a society be flexible and open to this new frontier, addressing the issues with an astute eye towards optimizing the human health and well-being that these technologies promise to provide while mitigating any harmful effects, both on the individual and for society at large.

By incorporating ethical guidelines at each stage of the investigative and implementative process, the health and well-being of those who stand to benefit from current and emerging technologies will be safeguarded. While the exact trajectory of this path cannot be predicted, acting in adherence with ethical principles will optimize the ability of the research to benefit all stakeholders. Robust oversight and ongoing efforts to educate the public will allow for a productive ongoing dialogue regarding each new finding. The expectation of knowledge sharing will allow scientists to evaluate, critique, and build upon each other's research. Using this proposed framework as a guide to contemporaneous as well as future research questions, some as yet unimagined, will safeguard the process of embryo research and allow current and future generations to reap its full benefit.

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APPENDIX A

HISTORICAL OVERVIEW: FEDERAL REGULATION OF EMBRYO RESEARCH IN THE UNITED STATES

In the years preceding the birth of the first IVF baby in 1978, the federal government became involved in a dialogue regarding the use of human embryos for research purposes. The first grant application for embryo research was submitted by Dr. Pierre Soupart to the NIH in 1973 and initially approved in 1975. Soupart was a professor in the department of obstetrics and gynecology and director of the center for Fertility and Reproductive Research at Vanderbilt University (60). The research involved obtaining oocytes from ovaries removed during routine gynecologic surgery and fertilizing them with donor sperm. Soupart planned on examining the in vitro growth of embryos for up to 6 days to determine if there were any morphologic or chromosomal abnormalities that could be discerned as a result of the process of fertilization outside of the body. His grant was initially approved by the NIH on scientific grounds in 1975. However, at the time of Soupart's grant application, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research was undergoing deliberations regarding just this type of research. This Commission was the precursor of the Ethics Advisory Board, and Soupart's proposal was the first to go before this Board in 1978. Funding for Soupart's research was ultimately declined on ethical grounds (61).

The Ethics Advisory Board (EAB) went on to produce a well-researched and thoughtfully considered document that summarized not only the world knowledge on in vitro fertilization to date, but also the various scientific and ethical arguments for and against the study of in vitro embryos. The Board concluded that "research involving in vitro fertilization is acceptable from an ethical standpoint." It did not specifically address embryo research, as it considered this research as inseparable from studies aiming to understand in vitro fertilization, embryo development and the newfound ability to achieve a live birth following IVF (62). The EAB faced significant political and public opposition. It met only twice, at which point it was defunded. Its charter expired in 1980, effectively imposing a moratorium on federal funding of embryo research which would last for twelve years.

The NIH established the Human Embryo Research Panel in 1994 to assist it in developing guidelines for funding preimplantation human embryo research (63). This panel concluded that creating embryos was justified when "the research by its very nature cannot otherwise be validly conducted" or when it is necessary for a study that is "potentially of outstanding scientific and therapeutic value." Requirements for research by this panel were founded on the assumption that the data could not be adequately obtained with less controversial methods. In addition, the panel's report called for the use of human embryos at the earliest stages and in the smallest numbers that would support the needs of the research. Except in very limited circumstances, the panel called for use of only those embryos that, although originally produced in the course of a reproductive effort, would ultimately have been discarded (63). Soon after this report was published, President Bill Clinton issued a statement disallowing the use of Federal funds for the formation of human embryos for research purposes, stating that "the subject raises profound ethical and moral questions as well as issues concerning the appropriate allocation of federal funds." This led to suspension of many of the approved experiments included in the five grants on human IVF research funded by NICHD earlier that year. Nevertheless, President Clinton's statement did support the Panel's recommendation to pursue research on existing embryos that remained in excess of the needs of couples pursuing IVF (64).

The NIH Human Embryo Research Panel's directives were short lived, as in 1995 Congress passed the Dickey-Wicker Amendment. This amendment prohibited the use of U.S. Department of Health and Human Services funds for "creation of a human embryo(s) for research purposes or research in which a human embryo(s) are destroyed, discarded, or knowingly subjected to risk of injury or death for research purposes." It was signed into law in 1996 (65). While not restricting private funds for embryo research, this amendment significantly curtailed embryo research due to the lack of access to Federal funding sources. In 1999, the National Bioethics Advisory Commission was charged with identifying "broad principles to govern the ethical conduct of research." It recommended federal support for stem cell research using embryos remaining after infertility treatment but opposing the formation of embryos specifically for research (66).

In 2000, the NIH interpreted the Dickey-Wicker Amendment in releasing guidelines for research on human embryonic stem cells (hESC), allowing for funding of selective research on hESC. It concluded that hESC must be derived with private funds and utilize cryopreserved embryos that were initially produced for the treatment of infertility. The embryos must be in excess of the reproductive desires of the donors and must be obtained with the consent of the donor. In effect, these new NIH guidelines partially reversed the Dickey-Wicker Amendment. However, this reversal was short-lived when President George W. Bush restricted federal funding to include only stem cell lines in existence on August 9, 2001 and derived from excess embryos produced solely for reproductive purposes and provided with informed consent of the donors. In keeping with past precedent, this restriction did not prohibit private and state funding of stem cell research.

In subsequent years, several attempts were made to expand federal funding for stem cell research. In 2005, the Stem Cell Research Enhancement Act (67) passed the House and Senate but was vetoed by President Bush. This Act would have expanded federal funding for stem cell research to include stem cells derived from embryos produced for, but subsequently not used in, the clinical in vitro fertilization process. Another attempt to pass this act (S.5) failed in 2007.

In 2009, then President Barak Obama cited the importance of research involving hESC as having the potential to lead to a better understanding and treatment of many disabling diseases and conditions. He issued Executive Order 13505 which revoked President Bush's restrictions on research which was limited only to the study of stem cell lines already in existence in 2001. It stated that "The purpose of this

order is to remove these limitations on scientific inquiry, to expand NIH support for the exploration of human stem cell research, and in so doing to enhance the contribution of America's scientists to important new discoveries and new therapies for the benefit of humankind" (9).

In response to Obama's more permissive approach to stem cell research, Sherley and Deisler brought a federal lawsuit against Kathleen Sebelius in her role as secretary of the Department of Health and Human Services. These two Ph.D.s, whose research involved the study of adult stem cells, sought to overturn the guidelines for public funding of human embryonic stem cell research that the NIH issued in response to Obama's Executive Order. Judge Royce C. Lamberth granted an injunction against federally funded embryonic stem cell research on the grounds that the guidelines for hESC research "clearly violate" the Dickey-Wicker Amendment. This went to appeal and judges in the U.S. District Court of D.C. found in favor of the defendant. The injunction was lifted in 2011. All subsequent appeals failed, culminating in the U.S. Supreme Court's refusal to hear this case in 2013 (68).

In April of 2016, amendments to the NIH Guidelines went into effect. Under the revised guidelines, which reflected many of the recommendations of an earlier National Academies study (69), individual human gene-transfer trials would be limited to cases in which NIH concurs with a request from an oversight body (such as an IRB) that has determined that a protocol would significantly benefit from recombinant DNA advisory committee review. However, in 2015 the NIH director issued a statement that the "NIH will not fund any use of gene editing technologies in human embryos" (10, 70, 71).

Currently, funding for embryo research is occurring at the state level to a limited degree. California, for example, has been funding embryo research and embryonic stem cell research since 2004 using funds from a state bond issued during the years when federal funding was limited (72). This funding measure will be up for renewal during the 2020 election. Connecticut, Maryland, New Jersey, and New York also produced funds for research that could not be federally funded (73).

In a 2017 report, the National Academies of Sciences, Engineering, and Medicine stated that "Heritable germline genome-editing trials must be approached with caution, but caution does not mean they must be prohibited. If the technical challenges are overcome and potential benefits are reasonable in light of the risks, clinical trials could be initiated, limited to only the most compelling circumstances and subject to a comprehensive oversight framework that would protect the research subjects and their descendants; and have sufficient safeguards in place to protect against inappropriate expansion to uses that are less compelling or less well understood." They recommend that clinical trials using heritable genome editing should be permitted only within a robust and effective regulatory framework that encompasses: 1) the absence of reasonable alternatives 2) restriction to preventing a serious disease or condition 3) restriction to editing genes that have been convincingly demonstrated to cause or strongly predispose to that disease or condition 4) restriction to converting such genes to versions that are prevalent in the population and are known to be associated with ordinary health with little or no evidence of adverse effects 5) the availability of credible preclinical and/or clinical data on risks and potential health benefits of the procedures (73).

At the present time, these recommendations cannot be acted upon at the Federal level due to restrictions put in place by the attachment of the Dickey-Wicker amendment to the appropriations bills of the Department of Health and Human Services. The U.S. FDA further clarified the restrictions with an ongoing prohibition for using federal funds for "research in which a human embryo is intentionally created or modified to include a heritable genetic mutation" (74). Congress responded by imposing restrictions on the FDA, prohibiting it from reviewing gene editing applications. This amendment has been attached to the annual appropriations bills for the Departments of Health and Human Services, Labor, and Education from 1996 and continues to be attached annually at the time of the publication of this report (74).

APPENDIX B

PUBLIC PERCEPTIONS TOWARDS EMBRYO RESEARCH

The magnitude of the public's role in guiding policy recommendations surrounding human embryo research is often debated. Attempts to discern the opinions and sentiments of the relevant public may occur via a robust dialogue, public forums and polling. A number of polls have been conducted which aim to understand the public's views towards emerging genetic technologies, as described below

STAT and the Harvard T.H. Chan School of public health conducted a poll of 1,000 randomly selected adults in 2016. It suggested that Americans have mixed views regarding embryo research. As an example, U.S. adults are almost evenly split when responding to the question of whether the federal government should fund scientific research on "changing the genes of unborn babies to reduce their risk of developing" certain serious diseases such as Huntington's disease, cystic fibrosis, or some types of muscular dystrophy" (75).

When further probed into whether such changes in the genes of unborn babies should be legal, 65% responded that they should not be legal, 26% felt that they should be legal and 9% state that they do not know. When looking at the subset of patients that claim to have some knowledge of this idea, 41% said it should be legal to change the genes of unborn babies to prevent serious diseases, and 54% of this subpopulation supported the federal funding of research in this area. In Americans who state that they have not heard or read much about this issue, only 39% were supportive of funding this type of research. It appears that as Americans have more exposure to embryo research technologies and the types of medical applications that may become available, they become more comfortable with the research and the clinical applications of these technologies as well as with government funding. Interestingly, the vast majority of Americans polled in the STAT/Harvard survey believe that decisions regarding whether or not to allow changing the genes of unborn babies should be made by scientists, physicians and other

technological experts. Less than 10% felt that these decisions should arise from government officials and policy makers.

In 2018, the Pew research Center conducted a similar poll of 2,537 U.S. adults (76). It asked a sample of the U.S. public to weigh in on the acceptability of gene editing technologies that are not currently in use. A majority of those surveyed, 72%, believe that gene editing would be an appropriate use of medical technology to treat a serious disease/condition that the baby would have at birth, and 60% felt gene editing would be appropriate to reduce the risk of a serious disease that could occur over a baby's lifetime. In light of the announcement of the first successful use of gene editing in human embryos to eliminate an inherited condition, the Pew poll asked Americans to consider the possibility that gene editing would involve testing on human embryos. A majority of those polled, 65%, said that this would be taking medical technology too far. It is interesting to note that while the majority favored gene editing, a minority supported the development of this technology via testing on human embryos, which is the only viable way to develop and research the technology. When asked about whether they would want to use gene editing to avoid serious diseases in their own children, 48% say yes. Interestingly, the percentage was lower (39%) among parents with children under age 18.

In the 2018 Pew survey, 87% of respondents who identified as high in religious commitment stated that if the development of gene editing would entail testing on human embryos, this would be taking the medical technology too far, versus 55% of those who identified as low in religious commitment. 79% of atheists responded that development of gene editing techniques that required testing on human embryos would be an appropriate use of medical technology. A majority of adults (73%) state that they believe that gene editing technologies would be used before the health effects are fully understood, and 70% worry that inequality would be prone to increase due to concerns that this technology would only be available to the wealthy.

The Pew survey asked respondents whether the idea of editing genes to give healthy babies a much-reduced risk of serious diseases and conditions is in keeping with other ways that humans have always tried to better themselves or whether "this idea is meddling with nature and crosses a line we should not cross." Americans' judgments on this question are closely divided, with 51% saying this idea is no different than other ways humans try to better themselves and 46% saying this idea crosses a line (76).

When looking at those with high science knowledge, the 2018 PEW survey found that 86% of U.S. adults in this group state that it is appropriate to use gene editing techniques to change a baby's genetic characteristics to treat a serious disease/condition that the baby would have at birth. This is in contrast with 58% of those surveyed who had low science knowledge (76).

Yet another survey, conducted by Hart Research Associates from May 14 to 17, 2015, queried a national sample of 1,019 adults regarding their feelings towards DNA modification as part of the Synthetic Biology Project at the Woodrow Wilson International Center for Scholars (WWCfS). In this poll, there was not a clear consensus regarding whether heritable DNA modification is a positive or negative. When pressed to give an opinion, 62% of adults have mixed feelings about this technology. The younger respondents felt more positive about heritable DNA modification. This survey also found that 45% of respondents favor a moratorium on the use of this technology in humans until ethical guidelines and safety controls are in place, and 43% of adults are undecided (54).

The most recent Gallup poll showed that the percentage of Americans that "personally believe that medical research using stem cells obtained from human embryos is morally acceptable" is generally trending upwards, from a low of 52% in 2002 when Gallup first conducted this poll, to 66% in 2018 (55). In May of 2017, a Gallup poll was conducted to survey U.S. adults regarding stem cell research. Of those surveyed, 61% felt the research to be morally acceptable, 33% felt it to be morally wrong, 3% stated it depended on the situation and 3% had no opinion. Regarding easing restrictions on federal funding of stem cell research, 14% preferred no restrictions, 38% preferred easing current restrictions, 22% favored keeping current restrictions, 19% preferred not to fund and only 7% had no opinion.

Prior Gallup polls asked Americans about their feelings towards embryos. 36% felt that the embryo is a human life that should be given the same protection as all other human lives, and 60% felt that the embryo has the potential for life, but is not the same as life, because it cannot develop on its own (55). That same year, 55% of respondents felt that the government should fund stem cell research on supernumerary embryos resulting from fertility treatment and 46% felt that the government should fund embryos produced expressly for stem cell research. A recent survey of over 11,000 individuals in eleven countries, including the United States, found that 60% of respondents favored intervention for prenatal therapy. Similar to previous studies, the authors found that there was much broader support for interventions that aimed to prevent disease in newborns than for those that led to increased intelligence or other changes that were perceived as non-medical enhancements (77).

In late 2018, AP-NORC conducted a an online and telephone poll of 1,067 adults about their attitudes towards the technology that could be used to edit the genes of human embryos (78). The results were similar to previous studies, with 71% of respondents favoring using technology to edit the genes of embryos to prevent an incurable or fatal disease that a child would inherit. Additionally, 67% of respondents would favor using this technology to reduce the risk of diseases such as cancer that may develop later in life, and 65% favor using this technology to prevent a non-fatal condition such as blindness. When asked about the use of taxpayer money to finance testing on human embryos to develop these gene editing technologies, 48% of those polled were opposed. This number depended upon political affiliation, with 61% of Republicans versus 3% of Democrats opposing the use of taxpayer money to finance the testing. Of those polled, 88% thought it would be somewhat or very likely that gene editing would be used for unethical reasons, and 86% thought it would be somewhat or very likely that gene editing would have unintended effects on human evaluation. Conversely, 87% felt that gene editing would be somewhat or very likely

to lead to other medical advances, and 63% thought it very or somewhat likely that gene editing would be adequately tested to ensure its safety before it was used.

While several polls have attempted to gauge the opinion of the population of the United States towards embryo research, they have been limited by the number of adults surveyed and the breadth of the questions answered. One key finding is the impact that lack of knowledge regarding these technologies has on perceptions regarding their moral acceptability. This speaks to the importance of an educated public in making decisions that will profoundly affect both research and clinical applications of this rapidly evolving field.

APPENDIX C

Current research on gene editing in human embryos

- Overview of Crispr/Cas9 (79)
  - Method of utilizing endonucleases to generate targeted double stranded DNA breaks, resulting in activation and recruitment of cellular enzymatic DNA repair machinery (via non-homologous end joining and/or homologous recombination)
  - Options:
    - Embryo editing: embryos injected with editing system, then screened to select embryos with correct edit/no off-target effects (80, 81)
    - Editing of male and female germ cells (17)
    - Editing of pluripotent stem cells (this work is in mice; not yet performed in human stem cells)
  - Possible uses:
    - Germline modification for genetic disease correction
    - Germline selection of nonmedical conditions/traits (obviously more controversial)
    - Research to understand fundamental questions of developmental biology
  - Major concerns include:
    - off-target effects (unspecific activity at other genomic locations)
    - low efficiency (generation of mosaic embryos and/or inaccurate DNA repair)
      - mosaicism in particular would make PGD difficult in edited embryos
    - germ line gene modification is a major ethical concern (70)
      - made "without the consent of future generations"
      - no long-term follow-up data available
      - will result in modification of the genome
      - research involves embryos
- Selected studies of interest:
  - Liang et al. (80) reported the first use of CRISPR/Cas9-mediated gene editing in human cells in 2015 (3PN zygotes, human beta globin protein (HBB; mutations in HBB responsible for beta thalassemia)
    - Major concerns: Low efficiency of homologous recombination-directed repair; edited embryos were mosaic; off-target effects were observed
  - Kang et al. (81), in the second reported use of CRISPR/Cas9 for embryo editing, used CRISPR/Cas9 to mutate CCR5 (gene responsible for HIV resistance in some individuals) in 3PN zygotes
    - Again, low efficiency and off-target effects
  - Ma et al (17) (U.S.-based team) performed CRISPR/Cas9 gene editing studies without donated embryos; rather, donated oocytes were used along with sperm from a male donor with MYBPC3 mutation (which results in hypertrophic cardiomyopathy)
    - Major concerns: high CRISPR-Cas9 based repair efficiency and homology-directed repair efficiency (via activation of endogenous DNA repair response) without mosaicism or off target effects, but insertions/deletions still apparent at DNA break sites

Use of stem cells derived from human embryos

- Overview:
  - Human embryonic stem cells (hESC): derived from early embryos (typically from ICM of blast-stage); first established in culture in 1998 (82)
    - Can differentiate into somatic tissues but not extraembryonic tissues (i.e. placenta, membranes), pluripotent, not totipotent
    - Procurement typically occurs in the context of infertility treatment (discarded or spare IVF embryos), though IVF embryos have been specifically produced for stem cell isolation (83)
    - Efficiency of derivation is improving (from <5% of donated embryos will result in hESC line in a 2007 study, to up to 50%) (84, 85)
- Ethical considerations (85)
  - "Personhood:" embryo as a "person" versus "non-person" and moderate views (i.e. embryo has "real but low" moral value"
  - Production of embryos for use solely for research
  - Use of aneuploid embryos for derivation of hESC lines
  - Restrictive guidelines may limit development of potentially beneficial therapies
  - "Slippery slope" argument: will lead to more "undesirable" practices
  - Principal of "subsidiarity": do alternatives exist?
- Potential uses: transplant medicine, toxicology, research on pregnancy loss/embryonic aging/infertility
  - Progress in particular has been in treatment of macular degeneration (86)
- Regulatory considerations: differ between countries
- Selected studies of interest
  - Much research has focused on using ESCs to understand pluripotency (87)
  - Major milestone was the derivation of stem cells via somatic cell nuclear transfer (nucleus from adult donor cell into human oocyte with nucleus removed), achieved in 2013 (88)
  - Additional major milestone: the discovery of induced pluripotent stem cells (iPSC)—returning adult cells to embryonic-like state, offering potential limitless supply

of patient-matched pluripotent cells without ethical dilemmas
    - In mice in 2006 (25)
    - In human cells in 2007 (89, 90)
  - Scope of use in reproductive medicine research and limitations reviewed by ESHRE working group in 2015 (91)

Research on aneuploidy and mosaicism

- Prevalence: may be common
  - In a systematic review of 815 embryos: 73% mosaic (59% diploid-aneuploid mosaic and 14% aneuploid mosaic) (92)
- Challenges:
  - Mosaicism plays a prominent role in misdiagnosis of CCS-screened euploid embryos (though clinically recognizable error rate <1%) (93)
  - Literature reflects concern/controversy about PGS accuracy
    - Gleicher et al. (94)
      - Re-biopsy of 11 aneuploid embryos; only 2/11 were identically assessed
      - 5/8 transfers of aneuploid embryos resulted in chromosomally normal pregnancies
      - Descriptive study, not powered to achieve statistical significance
    - Mir et al (95)
      - Blinded comparison of blastomere and trophoectoderm biopsy using array-CGH in aneuploid embryos: high concordance with whole blastocyst results
    - Capalbo et al. (96): high accuracy of diagnosis with blastocyst stage PGS coupled with 24-chromosome molecular karyotyping analysis
  - Interpretation of mosaic results is difficult b/c transfer of mosaic embryos has resulted in live births (94, 97, 98)
    - Potential mechanisms (98)
      - Primary misdiagnosis
      - Allocation of aneuploidy in trophectoderm
      - Cell growth advantage of diploid cells
      - Lagging of aneuploid cell division
      - Extrusion or duplication of aneuploid chromosomes
      - Abundance of DNA repair gene products
- Clinical management strategies (99)
  - Preferentially transfer euploid embryos
  - Genetic counseling including discussion of risk of undetected aneuploidies, IUFD, uniparental disomy, affected child
  - Preferentially transfer certain mosaics over others (2, 7, 13–16, 18, 21 may pose most risk of affected child)
  - Encourage another cycle before transferring mosaics

Latest articles on mitochondrial transfer and somatic cell nuclear transfer (if anything recent)

- Mitochondrial transfer (100, 101)
  - Uses:
    - alternative to germline gene therapy for patients at risk of transmitting mtDNA-based disorders
      - important because utility of PGD in patients with mitochondrial disorders is limited (for systematic review see Hellebrekers et al (102)
    - potential therapy for infertility associated with increased maternal age
  - One study describes co-injection of donor cytoplasm with sperm/ICSI for patients with repeated IVF failures (1999) (103)
    - several pregnancies established before FDA established jurisdiction and required that applications for patient treatment be established as part of clinical trials
    - review of available reports and concerns for ooplasmic transfer techniques by Darbandi et al. (104)
  - Ethical concerns (100, 101)
    - Permanent germline changes
      - Little data available but systematic review/meta-analysis formally assessing risks of mitochondrial replacement on offspring in UK (105) suggests negative effects in 1 out of every 130 offspring
    - Children born after mtDNA transfer have genetic connection to three parents (though mtDNA component is small)
    - May be unethical to deny germline therapies to patients with debilitating/life threatening conditions
- Somatic cell nuclear transfer (also summarized in 2016 ASRM ethics committee opinion) (106)
  - Derivation of stem cells via transfer of nucleus from adult donor cell into human oocyte with nucleus removed
    - Live births already achieved in animals using artificial gametes
    - Hendriks et al.: only systematic review of SCNT and other technologies for development of artificial gametes available (no high quality meta analyses or RCTs), reviews 70 studies involving development of artificial gametes (107)
  - Multiple reports of cloning success in animal species (108–113) but few reports of success with human nuclear transfer ESCs:
    - Pioneering work developing hESCs done by Shoukhrat Mitalipov at OHSU in 2013 (89) using fetal dermal fibroblasts as nuclear donors
    - Subsequently, generation of SCNT-hESCs using dermal fibroblasts from 30- and 75 year -old males (114)

Research on embryo growth and development in the lab (including studies of the optimal conditions for maturing embryos)

- Major considerations (systematic review) (115)
  - Method of fertilization
    - ICSI versus IVF:
      - 2003 Cochrane review demonstrated no difference in pregnancy rates when ICSI was

used for non-male subfertility (only one study included) (116)
    - 2013 Cochrane review demonstrated no evidence that IMSI (ultra-high magnification sperm selection) improves CPR over ICSI (possibly ineffective intervention, more evidence needed) (117)
  - Advanced sperm selection: 2014 Cochrane review found insufficient evidence to recommend HA binding over conventional sperm selection (118)
- Culture environment
  - Coculture: Prospective randomized study with or without cumulus cell coculture in women with RIF demonstrated improved implantation (119)
  - Coincubation: 2013 Cochrane review showed that brief coincubation of sperm/oocytes may improve CPR/OPR (promising intervention; more evidence needed) (120)
  - Assisted hatching: a 2012 Cochrane review, statistically significant difference in CPR but no evidence of significant difference in LBR following AH; significant increase in MPR (promising intervention; more evidence needed) (121)
  - Media:
    - Systematic review of 22 RCTs of effects of culture media on IVF/ICSI success; pooling data did not reveal superior culture medium (122)
    - 2015 Cochrane review also found insufficient evidence to support or refute the use of any specific culture medium (123)
    - 2016 meta-analysis and systematic review of 20 RCTs also found insufficient evidence to recommend either sequential or single step media (124)
- Temperature, culture, and static versus dynamic environment
  - Oxygen concentrations: 2012 Cochrane review showed increased LBR associated with embryo culture using low oxygen concentrations (5%) compared with atmospheric (20%) (effective intervention) (125)
  - Small-volume, ART specific incubators (115)
  - Reduction of embryo manipulation (115)
  - Dynamic embryo culture system (115)
- Analytical techniques
  - PGS with FISH: 2006 Cochrane review showed LBR lower following IVF/ICSI with PGS using FISH compared with no PGS (ineffective intervention) (126)
  - Time lapse systems: 2015 Cochrane review found insufficient evidence to support time lapse systems over conventional incubation with respect to LBR/miscarriage/stillbirth/CPR (no conclusion possible due to lack of evidence) (127)
  - Metabolomic assessment of embryos: 2018 Cochrane review found no evidence to show that metabolomic assessment of embryos before implantation has any meaningful effect on rates LBR/OPR (128)
- Freezing
  - 2014 Cochrane review: vitrification increases CPR compared to slow freeze (promising intervention; more evidence needed) (129)