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Can I Call You Back? A Sustained Interaction With Biospecimen Donors To Facilitate Advances In Research

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I. INTRODUCTION

[1] "For the cure." This statement resonates throughout society and offers a simple reasoning for the conduct of biomedical research. It provides a strong impetus for advocates of biomedical research to pursue appropriations to support research hypotheses, advanced medical technologies, and targeted therapeutic strategies. Answering sophisticated medical questions, however, requires researchers and clinicians to have an adequate supply of materials necessary to facilitate their research endeavors. These materials—commonly referred to as biospecimens—may include frozen human embryos, tissue specimens, blood samples, buccal swabs, or exhaled breath condensate, all of which may be collected and stored in biobanks.[1]

[2] The use of human embryos for research purposes generated national attention on March 9, 2009, following the release of Executive Order (E.O.) 13505, titled "Removing Barriers to Responsible Scientific Research Involving Human Stem Cells."[2] E.O. 13505 recognized that

[1] *See Biobanking*, COLLINS DICTIONARY, http://www.collinsdictionary.com/dictionary/english/biobanking, *archived at* http://perma.cc/WQU4-Q5GD (last visited Oct. 9, 2015) (defining biobanking as "the practice of creating large-scale repositories of human biological material (e.g. blood, urine, tissue samples, DNA, etc.) designed to further medical research").

research involving human embryonic stem cells (hESCs) may have the potential to increase the understanding of and improve treatments for disabling diseases and conditions.[3] Further, the E.O. removed the limitations on federal funding for stem cell research to facilitate scientific inquiry for new discoveries and therapies.[4]

[3] Following the release of E.O. 13505, the National Institutes of Health (NIH) published guidelines for implementing it.[5] The National Institutes of Health Guidelines on Human Stem Cell Research indicate that informed consent may need to be obtained for research involving hESCs per 45 C.F.R. pt. 46.[6] The NIH Guidelines also outline specific requirements of the informed consent process for donors of human embryos for research purposes.[7] Since the implementation of E.O. 13505, the NIH has funded more than $577 million in hESC research.[8] In addition, 351 hESC lines have been created and are included in the NIH stem cell registry for research purposes.[9]

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[2] *See* Exec. Order No. 13,505, 3 C.F.R. 229 (Mar. 9, 2009) [hereinafter Executive Order].

[3] *See id.*

[4] *See id.*

[5] *See National Institutes of Health Guidelines on Human Stem Cell Research*, NAT'L INST. OF HEALTH http://stemcells.nih.gov/policy/pages/2009guidelines.aspx, *archived at* http://perma.cc/2YQF-5SWZ (last modified Apr. 12, 2015) [hereinafter NIH Guidelines].

[6] *See id.*

[7] *See id.*

[8] *See NIH Funding for Embryonic & Non-Embryonic Stem Cells,* OATH OF GOD MINISTRIES, http://www.oathofgodministries.com/nih-funding-for-embryonic-non-embryonic-stem-cells/, *archived at* http://perma.cc/V9D3-MWU6 (last visited Oct. 9, 2015).

[4] While the scientific interest in—and federal funding for—research using hESCs has increased, the use of human embryos and other biospecimens for stem cell research and unforeseen future research has been the subject of debate. This debate stems from inquiries regarding how to best protect an individual's autonomy without impeding research aimed at finding "the cure" for complex diseases. The majority of commentaries proposing strategies to protect an individual's autonomy reflect a similar underlying principle: improving informed consent.

[5] Over the years, there have been several strategies proposed to improve the informed consent process related to the use of biospecimens—including donated human embryos—for unforeseen future research. These strategies include proposed modifications to federal and state regulations,[10] identifying consent models with applicability to unforeseen future research,[11] and altering the language of consent forms given to research participants to facilitate an informed decision about participation in research studies.[12] In addition, these strategies aim to prevent stigmatization, while also seeking to promote an individual's autonomy by affording an increased control over the use of their biospecimens.[13] Concerns of stigmatization reflect the notion that genomic data generated from an individual's biospecimens may result in a person or group of persons being stigmatized if their genetic makeup is linked to

[9] *See NIH Human Embryonic Stem Cell Registry*, NAT'L INST. OF HEALTH, http://grants.nih.gov/stem_cells/registry/current.htm, *archived at* http://perma.cc/XE54-ANBQ (last visited Oct. 9, 2015).

[10] *See* Christian M. Simon et al., *Active Choice but Not Too Active: Public Perspectives on Biobank Consent Models*, 13 GENETICS IN MED. 821, 821 (2011).

[11] *See* Timothy Caulfield et al., *Research Ethics Recommendations for Whole-Genome Research: Consensus Statement,* 6 PLOS BIOLOGY 430, 431 (2008).

[12] *See* Simon et al., *supra* note 11, at 829.

[13] *See* Caulfield et al., *supra* note, at 434.

stigmatized diseases or research.[14]

[6] Recognizing that informed consent is a central tenet to conducting research with human subjects,[15] the Department of Health and Human Services (HHS) issued its first national regulations in 1974 governing the protection of human subjects in the research it supported.[16] In 1991, 14 additional federal departments and agencies adopted the rules set forth by HHS.[17] This "Common Rule" requires investigators supported by federal funds to obtain and document the informed consent of individuals—or their legally authorized representative—prior to participating in research.[18] However, the regulations comprising the Common Rule were developed four decades ago and—although they have been amended—have not kept pace with the increased sophistication of advanced scientific methodologies and technologies.[19]

[7] In July 2011, HHS released an Advanced Notice of Proposed Rulemaking (ANPRM), titled "Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators," which proposed to modify the

[14] *See* M. Dechênes et al., *Human Genetic Research, DNA Banking and Consent: A Question of 'Form'?,* CLINICAL GENETICS 221, 227 (2001).

[15] *See* 2 TRIALS OF WAR CRIMINALS BEFORE THE NUREMBERG MILITARY TRIBUNALS UNDER CONTROL COUNCIL LAW NO. 10 181 (1949)

[16] *See Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators*, 76 Fed. Reg. 44,512, 44,512 (July 26, 2011) [hereinafter ANPRM].

[17] *See id.*

[18] *See id.* at 44,517 (for the remainder of this paper, the term individual will encompass the use of the term legally authorized representative as it relates to obtaining informed consent).

[19] *See id.* at 44,512.

rules governing research involving human subjects.[20] Included in the proposed modifications is a requirement that an individual give written consent for the use of their collected biospecimens for unforeseen future research.[21] However, such consent need not be study-specific, and can be construed as a blanket consent allowing the individual's biospecimens to be used in open-ended, unforeseen future research.[22] Further, the broad consent form proposed in the ANPRM would include check-off boxes for special categories of research (e.g., creating a cell line, or reproductive research) given the unique concerns these categories may raise to the public, such as stigmatization.[23] This differs from the Common Rule where research using existing biospecimens can be conducted without consent from the donor as long as the biospecimens do not include any identifiable information.[24]

[8] Although proposing the implementation of a broad consent model for the unforeseen future research use of biospecimens, the identification of special categories of research creates a broad-tiered hybrid model of informed consent. This model—attempting to balance an individual's autonomy while facilitating biomedical research—hinders advances in research by facilitating stigmatization due to the identification of special categories of research. Rather than encouraging an individual's autonomy, the proposed broad-tiered hybrid model discourages donors from consenting to the use of their biospecimens for stigmatized conditions due to imperfect or insufficient information. Likewise, the proposed broad-tiered hybrid model facilitates stigmatization by decreasing the number of studies and investigators addressing stigmatized conditions due to the

[20] *See id.*

[21] *See* 76 Fed. Reg. 44,512, 44,515 (July 26, 2011).

[22] *See id.*

[23] *See id.* at 44,520.

[24] *See* 45 C.F.R. § 46.101(b)(4) (2012).

paucity of heterogeneous biospecimens available. In response to the ANPRM, this article proposes a modified broad consent model that creates sustained interaction between donors and biobanking facilities by allowing facilities to recontact donors for the future use of their biospecimens in unforeseen and potentially stigmatizing research. Demonstrating its applicability in reproductive medical research, this model strikes an appropriate balance between an individual's autonomy and advancements in biomedical research by providing the donor sufficient information to make an informed decision without excess administrative burden on researchers.

A. Biobanking and Reproductive Medicine: Continued Preservation or Donation and Innovation?

[9] A biobank refers to a stored collection of genetic samples that can be linked with medical, genealogical, or lifestyle information from specific population(s) which is gathered using a process of generalized consent.[25] Although all biobanks fall under this definition, they differ in their functionality as related to biomedical research. A biobank may collect their own specimens and data in order to conduct research or rely on researchers at multiple sites to perform biospecimen collections and subsequently serve a role in aggregating the biospecimens for future research use.[26] Further, some biobanks—including the Coriell Personalized Medicine Collaborative[27]—serve a dual purpose in that they

[25] *See* SECRETARY'S ADVISORY COMM. ON GENETICS, HEALTH, AND SOC'Y, POLICY ISSUES ASSOCIATED WITH UNDERTAKING A NEW LARGE U.S. POPULATION COHORT STUDY OF GENES, ENVIRONMENT, AND DISEASE 16 (2007).

[26] Susan M. Wolf et al., *Managing Research Results and Incidental Findings in Genomic Research Involving Biobanks & Archived Datasets*, 14 GENETICS IN MED. 361, 363 (2012).

[27] *See CPMC FAQs*, CORIELL PERSONALIZED MEDICINE COLLABORATIVE, https://cpmc.coriell.org/about-the-cpmc-study/cpmc-faqs, *archived at* https://perma.cc/W233-KU4J (last visited Oct. 5, 2015).

conduct their own research while also aggregating and distributing data to investigators throughout the world.[28]

[10] Biobanks are a critical "resource for basic, epidemiological, and transnational research"[29]—including genome-wide association studies which facilitate the identification of genetic markers of disease.[30] According to the National Bioethics Advisory Commission, an estimated 282 million human biospecimens[31] were being stored in the United States as of 1998. Further, facilities accumulated stored biospecimens at a rate of 20 million cases per year.[32] Biobanks are diverse in the types of biospecimens stored (e.g., breast or brain tissue) and in the types of diseases they target (e.g., cancer or mental illness).[33] Given the number and diversity of samples stored, biobanks are a valuable resource to researchers focused on understanding the etiology of a particular disease and identifying novel strategies to prevent, diagnose, and treat diseases and their associated co-morbidities.

[11] As technology and our understanding of human biology have

[28] *See* William McGeveran et al., *Deidentification and Reidentification in Returning Individual Findings from Biobank and Secondary Research: Regulatory Challenges and Models for Management*, 13 MINN. J. L. SCI. & TECH. 485, 488 (2012).

[29] Laura M. Beskow & Elizabeth Dean, *Informed Consent for Biorepositories: Assessing Prospective Participants' Understanding and Opinions*, 17 CANCER EPIDEMIOLOGY BIOMARKERS & PREVENTION 1440, 1440 (2008) [hereinafter Beskow & Dean].

[30] *See, e.g.*, Stephen J. O'Brien, *Stewardship of Human Biospecimens, DNA, Genotype, and Clinical Data in the GWAS Era*, 10 ANN. REV OF GENOMICS AND HUM. GENETICS 193, 193 (2009).

[31] *See* NAT'L BIOETHICS ADVISORY COMM'N, RESEARCH INVOLVING HUMAN BIOLOGICAL MATERIALS: ETHICAL ISSUES AND POLICY GUIDANCE 13 (1999).

[32] *See id.*

[33] *See* Kimberly J. Cogdell, *Saving the Leftovers: Models for Banking Cord Blood Stem Cells*, 39 U. Mem. L. Rev. 229, 234 (2009) (citing Lori B Andrews, *Harnessing the Benefits of Biobanks*, 33 J.L. MED. & ETHICS 22, 23 (2005)).

matured, so has the use of biobanks. One area of scientific and technological development that has benefited from biobanking is reproductive medicine, as it relates to procreation via assisted reproductive technologies (ART). The processes of *in vitro* fertilization (IVF) include "ovulation induction, egg retrieval, fertilization, and embryo transfer."[34] From the first recorded attempt of IVF,[35] to the first IVF birth from cryogenically frozen embryos, the successful use of ARTs in facilitating procreation has increased as the technology has become more refined.[36] IVF is an intricate process that can be both physically and mentally taxing for women. To protect women's health and family welfare, "[t]he current procedure of extracting and fertilizing multiple eggs" reduces "the number of times [women] may need to undergo the procedure."[37]

[12] As the processes and procedures of IVF have become more refined, the number of cryogenically frozen embryos has increased.[38] Since the late 1970s, there have been nearly 400,000 embryos that have been frozen and stored.[39] Of these, only 2.8% have been designated by patients for use in research.[40] Research using hESCs derived from frozen

[34] Emilie W. Clemmens, *Creating Human Embryos for Research: A Scientist's Perspective on Managing the Legal and Ethical Issues*, 2 Ind. Health L. Rev. 95, 96 (2005).

[35] *See* Maggie Davis, *Indefinite Freeze?: The Obligations a Cryopreservation Bank Has to Abandoned Frozen Embryos in the Wake of the Maryland Stem Cell Research Act of 2006*, 15 J. HEALTH CARE L. & POL'Y 379, 382 (2012).

[36] *See id.* at 383 (citing Margie Mietling Eget, *The Solomon Decision: A Study of* Davis v. Davis, 42 MERCER L. REV. 1113, 1115 (1991)).

[37] *See* Clemmens, *supra* note 34, at 97.

[38] *See* Davis, *supra* note 35, at 383.

[39] *See id.* at 379.

[40] *See id.*

human embryos has gained significant interest over the past 15 years, as researchers predict that hESCs may be used to treat various disease conditions and to better understand the biological processes underlying reproductive and regenerative medicine.[41] The use of hESCs in medical research became increasingly important following the release of E.O. 13505, which permits embryos remaining after infertility treatment to be used in creating hESC lines.[42] Given the ability to use federal funding to support hESC research, it is anticipated that the number hESC lines will increase.[43]

[13] As there is increased interest by investigators in working with hESCs, it is reasonable to conclude that there will be a need for an increased supply of frozen human embryos to derive hESCs for research. As data indicate that the "vast majority of stored embryos" are "held for family building,"[44] the question arises as to where investigators requiring frozen human embryos for research can acquire them. This question underlies the conundrum that exists with respect to the disposition of frozen human embryos following family completion. This quandary includes the question of whether frozen human embryos should be preserved indefinitely due to abandonment, discarded,[45] or donated for research.[46]

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[41] *See* Ethics Comm. of the Am. Soc'y for Reproductive Med., *Donating Embryos for Human Embryonic Stem Cell (hESC) Research: A Committee Opinion*, 100 FERTILITY & STERILITY. 935, 935 (2013) [hereinafter ASRM Ethics Comm.].

[42] *Id.* at 936.

[43] *See id.*

[44] DAVID HOFFMAN ET AL., HOW MANY FROZEN HUMAN EMBRYOS ARE AVAILABLE FOR RESEARCH? (2003).

[45] A.D. Lyerly et al., *Decisional Conflict and the Disposition of Frozen Embryos: Implications for Informed Consent,* 26 HUM. REPROD. 646, 646 (2011).

[14] Legal scholars suggest that indefinitely freezing embryos—specifically those that have been abandoned[47]—is both impractical and immoral.[48] They argue that the lack of a definitive disposition for abandoned embryos may result in crysopreservation banks incurring financial costs as a result of preserving the embryos.[49] Facilities will likely shift these costs onto persons undergoing IVF, in order to defray the costs incurred by storing abandoned embryos.[50] In addition to concerns about practicality, indefinitely freezing abandoned embryos may be considered morally reprehensible[51] and result in litigation.[52]

[15] Whether an embryo should be discarded poses a significant problem for cryopreservation banks faced with determining if an embryo should be indefinitely stored. To bring uniformity to embryo disposition, legal scholars suggest imposing a statutorily defined period, forcing couples to make a choice about the disposition of their embryos or be

[46] Donation of human embryos to couples seeking fertility treatment is beyond the scope of this paper and will not be addressed.

[47] *See* Davis, *supra* note 35, at 380 n. 11 (defining an abandoned embryo as a "cryogenically stored human embryo whose progenitors have fallen out of contact with the cryopreservation storage facility without a forwarding address or directive to either dispose or donate the embryos.") (citing Paul C. Redman II & Lauren Fielder Redman, *Seeking a Better Solution for the Disposition of Frozen Embryos: Is Embryo Adoption the Answer?*, 35 TULSA L.J. 583, 583–84 (2000)).

[48] *See id.* at 396.

[49] *See id.*

[50] *See id.* at 396–97.

[51] *See id.* at 397 (citing I. Glenn Cohen, *The Right Not To Be a Genetic Parent?*, 81 S. Cal. L. Rev. 1115, 1186 (2008) (discussing the Catholic belief that it is "a sin to destroy or indefinitely freeze preembryos").

[52] *See* Davis, *supra* note 35, at 397 (citing *Doe v. Obama*, 631 F.3d 157, 164 (4th Cir. 2011)).

subject to a predetermined outcome.[53] The American Society for Reproductive Medicine (ASRM) suggests that ART programs develop program-specific policies focused on the disposition of embryos. However, in the absence of program-specific policies, ASRM proffers that it is ethically acceptable to consider embryos abandoned if there are no written instructions from the couple regarding disposition, diligent efforts have been made to contact the couple, and it has been at least 5 years since contact has been made.[54]

[16] In addition to the options of indefinitely freezing or discarding, frozen and/or abandoned embryos may be donated for research purposes. This option has been met with divergent views. Legal scholars suggest that abandoned frozen human embryos be donated for research, as donation supplies research facilities with the embryos needed without having to create them for the sole purpose of research.[55] Doing so would also alleviate the burden of having more couples affirmatively consent to have their unused and/or unwanted embryos donated for research.[56] In contrast, the ASRM contends that abandoned embryos should not be used for research unless the patient(s) had previously given consent.[57] Guidance from the ASRM indicates that abandoned embryos should be used for hESC research only if patient(s) were informed of the possibility that their embryos may be used for hESC research and provided their consent to

[53] *See id.* at 398.

[54] *See* Amato, P; Brzyski et al., *Disposition of Abandoned Embryos: A Committee Opinion*, 99 FERTILITY & STERILITY 1848, 1849 (2013).

[55] *See* Davis, *supra* note 35, at 381 (citing Natalie R. Walz, *Abandoned Frozen Embryos and Embryonic Stem Cell Research: Should There Be A Connection?*, 1 U. ST. THOMAS J.L. & PUB. POL'Y 122, 124 (2007) (suggesting that abandoned frozen embryos be made available for embryonic stem cell research)).

[56] *See id.* at 149–52.

[57] *See* ASRM Ethics Comm., *supra* note 41, at 938.

such use.[58]

[17] The perspective of ART patients is critical to determining an appropriate disposition for frozen human embryos. Evidence suggests that patients' undergo considerable stress in attempting to make a decision, resulting in the inclination to perpetually freeze the embryo.[59] For example, McMahon and colleagues found that approximately 70% of patients with embryos delayed their decision regarding disposition for up to 5 years.[60] Data also demonstrate that approximately 40% of patients having completed childbearing were unable to determine a preferred disposition of their excess embryos.[61]

[18] In addition to these data, recent evidence from Lyerly and colleagues provides further insight into the decisional conflict underlying the disposition of frozen human embryos.[62] In a survey of 1,005 individuals with cryopreserved embryos, 81.3% indicated that at the time of freezing they had specific intentions as to the disposition of their embryos.[63] Regarding the individuals' current intentions, 14.6% indicated that they were very/somewhat likely to keep their embryos frozen forever with 49.9% indicating that they were very/somewhat likely to donate their

[58] *See id.*

[59] *See* Sheryl de Lacey, *Parent Identity and 'Virtual' Children: Why Patients Discard Rather than Donate Unused Embryos*, 20 HUM REPROD. 1661, 1661 (2000).

[60] *See* Catherine McMahon et al., *Mothers Conceiving Through In Vitro Fertilization: Siblings, Setbacks, and Embryo Dilemmas After Five Years*, 10 REPROD TECH 131, 134 (2000).

[61] *See* Anne Lyerly et al., *Fertility Patients' Views About Frozen Embryo Disposition: Results of a Multi-institutional U.S. Survey*, 93 FERTILITY & STERILITY 499, 506(2010).

[62] *See* Lyerly, *supra* note 45, 646.

[63] *See id.* at 651.

frozen embryos for research.[64] In assessing the underlying cause of fertility patients' views regarding frozen embryo donation, data indicate that 47.8% of patients believed that they did not have enough information regarding what happens to embryos donated for research.[65] Taken together, these data highlight the necessity of an informed consent process that adequately addresses patients' needs regarding donation and future research uses of frozen human embryos.

B. Human Subjects Research Protection

[19] Federal regulations governing research involving human subjects[66]—including those underlying informed consent—are based primarily on recommendations from the National Commission for the Protection of Human Subjects in Biomedical and Behavioral Research.[67] Originally implemented by HHS, these regulations have since been adopted by 14 other federal departments and agencies as a Common Rule.[68] The Common Rule applies to all human subjects' research that is conducted, supported, or subject to regulation by any federal department or agency which takes appropriate administrative action to make the policy applicable to such research.[69]

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[64] *See id.*

[65] *See id.* at 652.

[66] *See, e.g.*, 45 C.F.R. § 46.101 (2014).

[67] *See* Marshall B. Kapp, *A Legal Approach to the Use of Human Biological Materials for Research Purposes,* 10 RUTGERS J. L. & PUB. POL'Y 1, 5 (2013); *see also* NAT'L COMM'N FOR THE PROT. OF HUMAN SUBJECTS OF BIOMEDICAL & BEHAVIORAL RESEARCH, DEP'T OF HEALTH, EDUC., & WELFARE, THE BELMONT REPORT: ETHICAL PRINCIPLES FOR THE PROTECTION OF HUMAN SUBJECTS OF RESEARCH, http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.html, *archived at* http://perma.cc/58DP-GWRY (April 18, 1979) [hereinafter BELMONT REPORT].

[68] *See* 76 Fed. Reg. 44,512, 44,512 (July 26, 2011).

[20] Federal regulations define a human subject as "a living individual about whom an investigator (whether professional or student) conducting research obtains (1) [d]ata through intervention or interaction with the individual, or (2) [i]dentifiable private information."[70] The Common Rule requires investigators supported by federal funds to obtain and document the informed consent of individuals or their legally authorized representative prior to participating in research protocols.[71]

[21] Investigators seeking informed consent should only do so under circumstances providing an individual a sufficient opportunity to consider whether they should participate in the study.[72] Informed consent documents and procedures should be in language understandable to the individual, and should not include any exculpatory language requiring an individual to waive any of their legal rights or releases the investigator,

[69] *See* 45 C.F.R. § 46.101(a) (2014). Research is defined as "a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge." *Id.* at § 46.102(d).

[70] *Id.* at § 46.102(f) (defining "intervention" as including "both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes;" identifying "interaction" as including "communication or interpersonal contact between investigator and subject;" and defining "private information" as "information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.").

[71] *See id.* at § 46.102(c) (defining "legally authorized representative" as "an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research.").

[72] *See id.* at § 46.116.

sponsor, institution, or its agents from liability for negligence.[73] Further, the possibility of coercion or undue influence to the individual should be minimized.[74]

[22] The Common Rule sets forth basic elements that investigators must include when seeking participation in a research study. Basic elements of informed consent include a statement indicating that the study involves research, an explanation of the purposes of the research, the expected duration of participation, a description of the procedures to be followed, and identification of any experimental procedures.[75] Further, the individual must be provided a description of any reasonably foreseeable risks[76] and/or benefits[77] associated with the study and a disclosure of any alternative procedures or alternative treatments that may be advantageous to the individual.[78] Individuals must also be provided a description of how confidentiality will be maintained[79] and an explanation of whom to contact for questions about the research, the individual's rights, and research-related injuries.[80] With respect to research-related injuries, individuals must also be provided information as to whether compensation or any medical treatments are available if injury occurs.[81] Informed consent

[73] *See* 45 C.F.R. § 46.116 (2014).

[74] *See id.*

[75] *See id.* at § 46.116(a)(1).

[76] *See id.* at § 46.116(a)(2).

[77] *See id.* at § 46.116(a)(3).

[78] *See* 45 C.F.R. § 46.116(a)(4) (2014).

[79] *See id.* at § 46.116(a)(5).

[80] *See id.* at § 46.116(a)(7).

[81] *See id.* at § 46.116(a)(6).

documents must also include a statement that an individual's participation is voluntary, that they may withdrawal participation at any time, and that refusal to participate or withdrawal will not result in any loss of benefits or penalties.[82]

[23] Central to research involving human subjects is the requirement that research protocols undergo Institutional Review Board (IRB) review and receive IRB approval.[83] IRBs are empowered to review, approve,

[82] *See id.* at § 46.116(a)(8); *see also id.* at § 46.116(b)(1)–(6) (citing additional elements of informed consent that shall be provided to individuals or their representatives, when appropriate: "(1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable; (2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent; (3) Any additional costs to the subject that may result from participation in the research; (4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject; (5) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject; and (6) The approximate number of subjects involved in the study.").

[83] *See* 45 C.F.R. § 46.111 (2014) (identifying the criteria necessary for IRB approval: "(a) In order to approve research covered by this policy the IRB shall determine that all of the following requirements are satisfied: (1) Risks to subjects are minimized: (i) By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes. (2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility. (3) Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children,

disprove, and—if necessary—require modification of a research protocol to secure approval.[84] Included in the IRB approval process of human subjects research is a review of the research protocol, including consent documents required for participant inclusion.[85] With respect to informed consent, an IRB is to assess and determine whether the information provided to an individual complies with the regulations governing informed consent.[86] "An IRB may waive the requirement for the investigator to obtain a signed consent … if … the research presents no more than minimal risk"[87] or the only record linking the individual and research is the consent document, which may pose the potential risk and harm of a breach of confidentiality.[88] Following approval, the research protocol is then subject to continuing IRB oversight and formal review at least annually.[89] However, there is a concern as how to strike an

prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons. (4) Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by §46.116. (5) Informed consent will be appropriately documented, in accordance with, and to the extent required by §46.117. (6) When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects. (7) When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data. (b) When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.").

[84] *See id.* at § 46.109(a).

[85] *See id.* at § 46.109(b).

[86] *See id.*

[87] *See id.* at § 46.117(c)(2).

[88] *See* 45 C.F.R. § 46.117(c)(1) (2014).

[89] *See id.* at § 46.109(e).

appropriate balance to ensure that individuals are informed of all the potential uses of their biospecimens without impeding biomedical research by creating administrative burden.

C. Applicability of the Common Rule to the Unforeseen Future Use of Biospecimens

[24] The Common Rule is applicable to the collection, storage, and use of frozen human embryos and other biospecimens, albeit in finite circumstances. Research involving biospecimens "obtained prospectively from living people . . . falls within the definition of human subjects research [as] it involves an 'intervention or interaction with' a living individual."[90] Guidance from the HHS Office for Human Research Protections (OHRP) further clarifies what constitutes human subjects research as it pertains to biospecimens.[91] OHRP indicates that "obtaining identifiable private information or identifiable specimens for research purposes constitutes human subjects research."[92] "Obtaining identifiable private information or identifiable specimens includes . . . but is not limited to . . . [the] us[e], stud[y], or analy[sis] for research purposes [of] identifiable private information or identifiable specimens . . . provided to investigators from any source . . . [including those] that were already in the possession of the investigator."[93] This includes research using human

[90] Leslie E. Wolf, *Advancing Research on Stored Biological Materials: Reconciling Law, Ethics, and Practice*, 11 MINN. J.L. SCI. & TECH. 99, 130 (2010) (quoting 45 C.F.R. § 46.102(f) (2014)).

[91] *See* OFFICE FOR HUMAN RESEARCH PROTS., U.S. DEP'T OF HEALTH & HUMAN SERVS., GUIDANCE ON RESEARCH INVOLVING CODED PRIVATE INFORMATION OR BIOLOGICAL SPECIMENS 1, http://www.hhs.gov/ohrp/policy/cdebiol.html, *archived at* http://perma.cc/VZ3C-5K8D (Oct. 16, 2008) [hereinafter OHRP BIOLOGICAL SPECIMENS GUIDANCE].

[92] *Id.* at 3–4 (emphasis omitted).

[93] *Id.* at 4 (emphasis omitted).

cell lines (e.g., hESCs) where the donor may be identified due to coding that retains identifiable information.[94]

[25] However, "private information [and] specimens [are] not [considered] to be individually identifiable when they cannot be linked to specific individuals by the investigator(s) either directly or indirectly through coding systems." [95] Research involving coded [96] human biospecimens therefore does not constitute human subjects research if the biospecimens "were not collected specifically for the currently proposed research project through an interaction or intervention with living individuals." [97] Additionally, for research involving coded human biospecimens to not be considered human subjects research, "the investigator(s) cannot [be able to] readily ascertain the identity of the individual(s) to whom the coded private information or specimens pertain."[98] Thus, *in vitro* research or *in vivo* animal research using hESCs retaining a link to identifiable information ordinarily would not be considered human subjects research if the investigator was unable to

[94] *See* OFFICE FOR HUMAN RESEARCH PROTS., U.S. DEP'T OF HEALTH & HUMAN SERVS., GUIDANCE FOR INVESTIGATORS AND INSTITUTIONAL REVIEW BOARDS REGARDING RESEARCH INVOLVING HUMAN EMBRYONIC STEM CELLS, GERM CELLS AND STEM CELL-DERIVED TEST ARTICLES 3, http://www.hhs.gov/ohrp/policy/stemcell.pdf, *archived at* http://perma.cc/2NJN-NDMJ (Mar. 19, 2002) [hereinafter OHRP STEM CELL GUIDANCE].

[95] OHRP BIOLOGICAL SPECIMENS GUIDANCE, *supra* note 91, at 4.

[96] Under the OHRP guidance, "coded" is defined as "1. identifying information (such as name or social security number) that would enable the investigator to readily ascertain the identity of the individual to whom the private information or specimens pertain has been replaced with a number, letter, symbol, or combination thereof (i.e., the code); and 1. a key to decipher the code exists, enabling linkage of the identifying information to the private information or specimens." *Id.* at 3.

[97] *Id.* at 4.

[98] *Id.* at 4.

access identifiable private information related to the cell line.[99]

[26] Biobanks facilitate the ability to obtain and share coded biospecimens for research without the need for informed consent via several mechanisms. For example, an investigator may enter into an agreement with the "key holder" of coded biospecimens which prohibits the release of coded information to the investigator until the individual is deceased.[100] This type of agreement is characterized as the honest broker concept.[101] In this role, the honest broker (biobank) collects and provides health information to researchers in such a manner that it is not reasonably possible for the researchers to identify the subjects.[102] The applicability of the honest broker concept as it relates to biospecimens and human subjects research has been further characterized by legal scholars. Here, an investigator may share previously collected biospecimens with one or multiple investigators.[103] As the subsequent investigator(s) did not obtain the biospecimens via interaction or intervention with the donors and—based on an agreement—does not and cannot receive personally identifiable information, the research would not be considered human subjects research or require informed consent.[104]

[27] In addition to the honest broker methodology, there may also be IRB-approved written policies and procedures for a biobank that prohibits

[99] *See* OHRP STEM CELL GUIDANCE, *supra* note 94, at 3.

[100] *See* OHRP BIOLOGICAL SPECIMENS GUIDANCE, *supra* note 91, at 7.

[101] *See* Rajiv Dhir, et al., *A Multidisciplinary Approach to Honest Broker Services for Tissue Banks and Clinical Data: A Pragmatic and Practical Model*, 113 CANCER 1705, 1707 (2008).

[102] *See id.*

[103] *See* Wolf, *supra* note 90, at 131.

[104] *See id.*

the release of the key to the investigators under any circumstances, until the individuals are deceased.[105] Such schemata refer to centralized biobanks that store biospecimens and assume the responsibility of ensuring that biospecimens are distributed and used in accordance with human subjects research regulations.[106]This approach is similar to the honest broker approach as there are agreements in place prohibiting the release of identifiable information.[107] However, the agreements protecting the identifiable information apply to any investigator seeking to use the biospecimens as opposed to being negotiated on an ad hoc basis.[108]

[28] Research using existing biospecimens may also be exempt from federal regulation if the biospecimens are publicly available, or if the information is recorded in such a manner that subjects cannot be identified—directly or indirectly—via linked subject identifiers.[109]

D. Modifying the Common Rule to Regulate the Use of Biospecimens in Unforeseen Future Research

[29] In July 2011, HHS released an ANPRM entitled "Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators."[110] The ANPRM proposes to modify the rules governing research involving human subjects.[111] The ANPRM indicates that the "current regulations

[105] *See* OHRP BIOLOGICAL SPECIMENS GUIDANCE, *supra* note 91, at 4.

[106] *See id.*; *see also* Wolf, *supra* note 90, at 131.

[107] *See* Wolf, *supra* note 90, at 131.

[108] *See id.*

[109] *See* 45 C.F.R. § 46.101(b)(4) (2014).

[110] 76 Fed. Reg. 44,512, 44,512 (July 26, 2011).

governing human subjects research were developed years ago" and "have not kept pace with the evolving human research enterprise," including "the proliferation of multi-site clinical trials and . . . research involving . . . biological specimen repositories."[112] The ANPRM recognizes

> biospecimens and data . . . collected for clinical use or purposes other than for the proposed research are often an important source of information and material for investigators, and the reuse of existing data and materials can be an efficient mechanism for conducting research without presenting additional physical or psychological risks to the individual . . . .[113]

Citing the Institute of Medicine, the ANPRM notes the importance of "'facilitat[ing] important health research by maximizing the usefulness of patient data associated with biospecimens banks . . . thereby allowing novel hypotheses to be tested with existing data and materials as knowledge and technology improve.'"[114]

[30] While recognizing the importance of research involving biospecimens, the ANPRM proposes to enhance human subjects protections by requiring written consent for biospecimens collected for purposes other than the currently proposed research.[115] In an effort to increase protections by modifying consent requirements, the ANPRM

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[111] *See id.*

[112] *Id.*

[113] *Id.* at 44,523–24.

[114] *Id.* at 44,524 (quoting NAT'L ACAD. OF SCIS., BEYOND THE HIPAA PRIVACY RULE: ENHANCING PRIVACY, IMPROVING HEALTH THROUGH RESEARCH 10 (Sharyl J. Nass et al. eds. 2009)).

[115] *See* 76 Fed. Reg. 44,512, 44,519 (July 26, 2011).

suggests investigators use and human subjects consent be obtained via a brief standard consent form.[116] The brief standard consent form would allow human subjects to agree to "permit future research" and "be broad enough to cover all biospecimens to be collected related to a particular set of encounters with an institution (e.g. hospitalization) or even to any biospecimens to be collected at any time by that institution."[117] Thus, "[t]he general rule would be that a person needs to give consent, in writing, for research use of their biospecimens, though that consent need not be study-specific, and could cover open-ended future research."[118] Although not study-specific, the "standardized general consent form would permit the subject to say no to all future research" and would have "check-off boxes" to allow the subject to determine the types of research that may be performed with their biospecimens, including but not limited to creating cell lines or reproductive research.[119]

[31] In addition to proposing the adoption of a brief, standardized consent form to cover unforeseen future research using a subject's biospecimens, the ANPRM also proposes that consent forms be improved. According to the ANPRM, federal regulations will facilitate the development of improved consent forms by "prescribing appropriate content that must be included in consent forms, with greater specificity . . . [and] restricting content that would be *inappropriate* to include."[120] The ANPRM also notes that improving consent forms would also require "limiting the acceptable length of various sections of a consent form; . . . prescribing how information should be presented . . . reducing institutional 'boilerplate' [language] . . . and . . . making available standardized

[116] *See id.*

[117] *Id.* at 44,515.

[118] *Id.*

[119] *Id.* at 44,519–20.

[120] 76 Fed. Reg. 44,512, 44,523 (July 26, 2011).

consent form templates."[121] Thus, the overall goal is to have broad, standardized consent forms (with special categories of research) that are streamlined—in both length and content—in order to facilitate the subject making an informed decision about the future use of their biospecimens. Prior to implementing rules requiring informed consent modifications, it is critical to assess the current models of obtaining informed consent and the attitudes of perspective research participants related to those models. Likewise, it is essential to determine whether modifying the rules governing informed consent would hinder research due to stigmatization.

II. INFORMED CONSENT IN UNFORESEEN FUTURE RESEARCH

[32] Informed consent is the hallmark of medical decision-making as related to the practice of medicine and the conduct biomedical research. Critical to the doctrine of informed consent is the ethical principle of respect for persons or autonomy. Pursuant to the Belmont Report, there are two ethical convictions underlying respect for persons: 1) "individuals should be treated as autonomous agents," and 2) those "with diminished autonomy are entitled to protection."[122] In order to respect autonomy, it is essential to give credence to an autonomous person's considered opinions and choices and to avoid obstructing their actions unless they are detrimental to the wellbeing of others.[123] Thus, repudiation of an autonomous person's considered judgments, withholding information necessary to make such judgments, or denying their freedom to act upon such judgments offends their autonomy.[124]

[33] In the context of human subjects research, respecting autonomy

[121] *Id.*

[122] BELMONT REPORT, *supra* note 67.

[123] *See id.*

[124] *See id.*

requires that human subjects are provided adequate information and that their participation is voluntary.[125] Autonomy takes on two distinct forms with regard to research involving biospecimens. In the first form, a human subject may consent to the collection and storage of their biospecimens and their use in a primary research study.[126] Thus, an individual may provide consent for the storage and use of cancerous tissue following excision in a primary research study assessing for biomarkers underlying the tissue's proliferative nature.

[34] In the second form, there is the difficult challenge of how to obtain informed consent for the use of an individual's biospecimens for unforeseen future research.[127] Scholars maintain that permission for use of biospecimens for unforeseen research may be considered valid only if the individual has been informed of the possibility of their use.[128] Notifying human subjects of the possibility that their biospecimens may be used in unforeseen future research is a rather simple task that may be satisfied with a blanket statement in a consent form. Although simple in the abstract, the adequacy of such an approach may be challenged as it does not divulge the potential uses of the biospecimens—including the benefits and risks—to allow an individual to make an informed decision.

[35] With respect to affording an individual the opportunity to make an informed decision, the quandary is how to protect autonomy given the difficulty—if not impossibility—of predicting all of the potential future

[125] *See id.*

[126] *See* Amy L. McGuire & Laura M. Beskow, *Informed Consent in Genomics and Genetic Research*, 11 ANN. REV. GENOMICS AND HUM. GENETICS 361, 361–81 (2010) [hereinafter McGuire & Beskow].

[127] *See id.*

[128] *See* Henry T. Greely, *Breaking the Stalemate: A Prospective Regulatory Framework for Unforeseen Research Uses of Human Tissue Samples and Health Information*, 34 WAKE FOREST L. REV. 737, 754 (1999).

research uses of an individual's biospecimens. Such a prediction is impractical, given the ever-changing developments in technology and scientific methodologies that may elucidate therapeutic targets for diseases. Technological and scientific innovations will further result in an insurmountable number of research questions and hypotheses that are impossible to predict. Additionally, consent forms including the use of biospecimens for unforeseen future research would require investigators to predict all of the potential future risks and benefits associated with such research in order to allow human subjects to make an informed decision about future use. To strike a balance between human subjects autonomy related to the use of their biospecimens in unforeseen future research and efficiency in biomedical research, three consent models applicable to biobanking have been proposed: broad consent, tiered consent, and study-specific consent.

A. Broad Consent for Unforeseen Future Research

[36] Broad consent requests that human subjects prospectively agree that their biospecimens may be used in appropriate unforeseen future research as determined by a biobank and/or related oversight body.[129] Researchers, ethicists, and legal scholars have argued that broad consent is inadequate and inapposite to the Common Rule as it does not inform individuals of what the unforeseen future research will entail or its potential risks and benefits.[130] For example, Árnason contends that the broader that consent is "the less informed it becomes[,] [and] [i]t is

[129] *See* Christian Simon et al., *Active Choice but Not Too Active: Public Perspectives on Biobank Consent Models*, 13 GENET. MED. 821, 821–31(Lippincott, Williams & Wlkins eds., 2011).

[130] *See id.* (citing David E. Winickoff & Richard N. Winickoff, *The Charitable Trust as a Model for Genomic Biobanks*, 349 NEW ENG. J. OF MED. 1180, 1180–84 (2003)); Timothy Caulfield et al., *Research Ethics Recommendations for Whole-Genome Research: Consensus Statement*, 6 PLOS BIOLOGY 430, 430–35 (2008); Mylène Deschênes et al., *Human Genetic Research, DNA Banking and Consent: A Question of 'Form'?*, 59 CLINICAL. GENET. 221, 224 (2001).

misleading to use the notion of informed consent for participation in research that is unforeseen and has not been specified in a research protocol."[131] Individuals providing broad consent for the use of their biospecimens in unforeseen future research therefore are considered to be giving their permission[132] as opposed to their informed consent as the research uses of their biospecimens cannot be described in detail.

[37] Despite these concerns, the World Health Organization (WHO) recommended investigators use blanket informed consent forms (broad consent) to facilitate their research.[133] Here, the WHO recognized blanket informed consent—allowing for future use of biospecimens in unspecified projects—as the most efficient and economical approach as it avoids the necessity for and costs associated with recontacting individuals before each new research project.[134] Likewise, the United Nations Educational, Scientific and Cultural Organization International Bioethics Committee concluded that a "system which required fresh consent would be extremely cumbersome and could seriously inhibit research and it is for this reason that a system of 'blanket consent' covering all forms of future medical research might be preferable. . . ."[135] Although broad consent may

[131] Vilhjálmur Árnason, *Coding and Consent: Moral Challenges of the Database Project in Iceland*, 18 BIOETHICS 27, 42 (2004).

[132] *See* Greely, *supra* note 128, at 752–54.

[133] WORLD HEALTH ORGANIZATION, PROPOSED INTERNATIONAL GUIDELINES ON ETHICAL ISSUES IN MEDICAL GENETICS AND GENETIC SERVICES (1998), http://whqlibdoc.who.int/hq/1998/WHO_HGN_GL_ETH_98.1.pdf, *archived at* http://perma.cc/4VM5-Y7QF.

[134] *See id.* at 13.

[135] UNITED NATIONS EDUC., SCI. AND CULTURAL ORG., HUMAN GENETIC DATA: PRELIMINARY STUDY BY THE IBC ON ITS COLLECTION, PROCESSING, STORAGE AND USE 1, 16 (2002), http://portal.unesco.org/shs/en/files/2138/10563744931Rapfinal_gendata_en.pdf/Rapfinal_gendata_en.pdf, *archived at* http://perma.cc/84E4-DRKE.

be more efficient for researchers with respect to the cost, quality, and quantity of future research, the question remains whether broad consent adequately protects human subjects' autonomy.

B. Tiered Consent for Unforeseen Future Research

[38] An alternative to broad consent is tiered or categorical consent. Presented at the time of the initial consent to participate in a biobank and future research, tiered consent allows human subjects to choose from a list of diseases (e.g., cardiovascular, cancer, developmental) or research capabilities (e.g., genomics, proteomics, hESC) in which their samples may be used in the future.[136] Using a tiered consent model, human subjects may also be afforded alternative options related to their biospecimens. These options may include consenting to whether their biospecimens can be shared among researchers, used for commercial purposes, used in an identifiable manner, and/or limited for the purposes of only conducting the primary study.[137] Scholars maintain that appropriate implementation of the tiered consent model requires that consent forms provide a maximum number of options (i.e., disease states, research methodologies) that are empirically informed and indicative of an individual's informational needs and preferred level of control over their biospecimens.[138] Doing so is considered to both respect and enhance autonomy by allowing human subjects to exert control over whether, how, with whom, and how much of their biospecimens are shared.[139]

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[136] *See* McGuire & Beskow, *supra* note 126.

[137] *See* Leslie E. Wolf & Bernard Lo, *Untapped Potential: IRB Guidance for the Ethical Research Use of Stored Biological Materials*, 26 IRB: ETHICS & HUMAN RESEARCH 1, 4 (2004).

[138] *See* Susanne B. Haga & Laura M. Beskow *Ethical, Legal, and Social Implications of Biobanks for Genetics Research*, 60 ADV. GENET. 505, 520 (2008) [hereinafter Haga & Beskow].

[39] Tiered consent has been criticized, however, due to the burdens it places on researchers.[140] Such burdens include (1) the need for biobanks to track and match research participants approved uses of their biospecimens with the research being proposed or performed,[141] (2) increased research costs,[142] and (3) delayed progress in elucidating and understanding the role of specific genes, proteins, and/or molecular mechanisms in co-morbid conditions due to the compartmentalization of research by individual diseases.[143] Thus, similar to the broad consent model, the challenge in implementing a tiered consent model is in striking an appropriate balance that respects an individual's autonomy without impeding biomedical research by overburdening a researcher.

C. Study-Specific Consent for Unforeseen Future Research

[40] Study-specific consent differs from broad and tiered consent models in that biobank participants are recontacted, provided information about the current study in which they are eligible to participate in, and asked to participate.[144] In doing so, study-specific consent is similar to informed consent obtained for a primary study as it provides individuals

[139] *See* Amy L. McGuire & Richard A. Gibbs, *Currents in Contemporary Ethics: Meeting the Growing Demands of Genetic Research*, 34 J. LAW. MED. ETHICS 809, 811 (2006).

[140] *See* Haga & Beskow, *supra* note 138 (citing William Grizzle et al., *Recommended Policies for Uses of Human Tissue in Research, Education, and Quality Control,* 123 ARCH. PATHOL. LAB. MED. 296, 299 (1999)).

[141] *See* Darren Shickle, *The Consent Problem Within DNA Biobanks*, 37 STUD. HIST. PHILOS. BIOL. BIOMED. SCI. 503, 516 (2006).

[142] *See* David Wendler, *One-time General Consent for Research on Biological Samples,* 332 BRIT. MED. J. 544 (2006).

[143] *See* Mark A. Rothstein, *Expanding the Ethical Analysis of Biobanks*, 33 J.L. MED. & ETHICS 89, 92 (2005).

[144] *See* ANPRM, *supra* note 16, at 44,524.

with detailed information about the current study, including the risks and benefits associated with participation.[145] However, study-specific consent has been considered impractical as related to unforeseen future research with biospecimens, due to the costs and logistical roadblocks associated with recontacting potential research participants.[146]

D. Human Subjects Perspectives Regarding Consent for Unforeseen Future Research

[41] In determining the type of consent model that strikes an appropriate balance between an individual's autonomy related to the unforeseen future use of their biospecimens without impeding biomedical research, it is critical to consider the perspectives of human subjects. There have been several empirical studies assessing human subjects' willingness to participate in research, the unforeseen use of their biospecimens in research, and their expectations regarding consent.

[42] In 2006, the NIH Department of Clinical Bioethics performed meta-analyses assessing patient willingness and preference with respect to consent for research using their biospecimens.[147] The NIH collected and subsequently reviewed data from 30 studies—consisting of more than 33,000 people—assessing the views of research participants, patients, families, religious leaders, and the general public.[148] Data revealed that respondents wanted to decide whether their biospecimens can be used for research purposes.[149] Additionally, of the 30 studies included in the meta-analysis, 20 studies investigated the willingness of individuals to donate

[145] *See* Simon, *supra* note 129, at 822.

[146] *See* ANPRM, *supra* note 16, at 44,524.

[147] *See* Wendler, *supra* note 142, at 544–47.

[148] *See id.* at 544.

[149] *See id.*

their biospecimens.[150] Of these 20 studies, 17 provided evidence demonstrating that approximately 80% of respondents would donate their biospecimens if asked.[151] The majority of respondents who were unwilling to donate were concerned with the methodologies used to obtain biospecimens as opposed to the possibility of the future use of the biospecimens for research purposes.[152] Regarding consent preferences, the NIH assessed data from six studies which revealed that 79-95% of respondents were willing to provide a one-time general (broad) consent for the use of their biospecimens in research.[153]

[43] Although criticized due to the lack of heterogeneity in the populations assessed, subsequent studies support the findings of the NIH.[154] Beskow and Dean identified that 85% of potential research participants "would allow their blood and information to be stored, indefinitely . . . for use in future research."[155] Additionally, data from Simon and colleagues assessing public perspectives on broad, tiered, and study-specific consent revealed that broad consent garnished the strongest support from potential biobank participants.[156] Participants in the study recognized that implementation of a broad consent model would result in them having less control over the use of their biospecimens.[157] However,

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[150] *See id.*

[151] *See* D.Wendell, *supra* note 142, at 544.

[152] *See id.* at 544–45.

[153] *See id.* at 546.

[154] *See* Laura M. Beskow & Elizabeth Dean, *Informed Consent for Biorepositories: Assessing Prospective Participants' Understanding and Opinions,* 17 CANCER EPIDEMIOL BIOMARKERS 1440, 1447 (2008).

[155] *Id.* at 1446.

[156] *See* Simon, *supra* note 129, at 9.

the participants believed that broad consent—in addition to being less costly and less burdensome for the participants—may result in "a larger and more diverse collection of samples and thus provide researchers with 'a broad amount of people of different backgrounds and . . . more to choose from.'" [158] Empirical research therefore suggests that human subjects prefer to exert some level of control over whether their biospecimens can be used in unforeseen future research, with the majority of indicating that a broad consent model adequately addresses that preference.[159]

E. Stigmatization and the Use of Biospecimens for Unforeseen Future Research

[44] Researchers, ethicists, and legal scholars have argued that informed consent, by protecting research participants' autonomy aids in preventing stigmatization. Stigma refers to a mark setting a person apart from others and links the marked person to characteristics that are undesirable.[160] Further, when a person or group of persons are linked to an undesirable characteristic, "rejection and isolation" of the stigmatized person or persons comes into play.[161] Therefore, stigma is a matter of degree and is contingent upon the strength or weakness with which a marked person can be linked to undesirable characteristics.[162]

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[157] *See id.*

[158] *Id.*

[159] *See Id.* at 13; *see also* ANPRM, *supra* note 16, at 44,524.

[160] *See* Bruce G. Link et al., *On Stigma and Its Consequences: Evidence from a Longitudinal Study of Men with Dual Diagnoses of Mental Illness and Substance Abuse,* 38 J. OF HEALTH & SOC. BEHAV. 177, 179 (1997).

[161] *Id.*

[162] *See id.*

[45] Stigmatization has commonly been associated with mental health disorders[163] (e.g., depression and addiction), human immunodeficiency virus (HIV),[164] and reproductive health.[165] Individuals therefore are concerned that their biospecimens may be used for unforeseen future research on stigmatized disorders or that they may be identified as someone with a predisposition to or undergoing treatment for a stigmatized disease.[166] Although some scholars maintain that public fear of discrimination is unwarranted due to a lack of reported cases of genetic discrimination,[167] this argument underscores the impact of stigmatization, which is distinct from discrimination. For example, with respect to HIV, stigma may affect decisions related to testing and seeking treatment for physical and psychological needs.[168] Additionally, couples capable of transmitting deleterious genes to their offspring may be deterred from considering ARTs.[169]

[46] Given the data that can be extracted from the use of an individual's biospecimens and the inherent risk of being associated with a stigmatized disease, there is growing concern regarding the unforeseen future use of

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[163] *See* Bruce G. Link, *A Modified Labeling Theory Approach in the Area of Mental Disorders: An Empirical Assessment,* 54 AM. SOC. REV. 400, 401 (1989).

[164] Ronald Bayer, *Stigma and the Ethics of Public Health: Not Can We but Should We*, 67 SOC. SCI. AND MED. 463, 464–66 (2008).

[165] Rebecca J. Cook & Bernard M. Dickens, *Reducing the Stigma in Reproductive Health*, 125 INT'L J. OF GYNECOLOGY AND OBSTETRICS 89, 89–92 (2014).

[166] *See* Lori B. Andrews, *Harnessing the Benefits of Biobanks*, 33 J L. MED. & ETHICS 2, 4 (2005).

[167] *See* Henry Greely, *Genotype Discrimination: The Complex Case for Some Legislative Protection*, 149 U. PA. L. REV. 1483, 1489–90 (2001).

[168] *See* Bayer, *supra* note 164, at 464.

[169] *See* Cook & Dickens, *supra* note 165, at 91.

biospecimens. An additional concern is that providing individuals with the opportunity to opt-out of studies focused on stigmatized conditions will impede research aimed at identifying the underlying causes of and treatments for these conditions.

F. Consent under the ANPRM: Striking an Appropriate Balance?

[47] As previously described, the ANPRM seeks to modify the rules governing informed consent as related to research involving human subjects.[170] The ANPRM recommends that human subjects provide their written consent indicating that their collected biospecimens can be used for unforeseen future research.[171] The ANPRM envisions the use of a broad, standardized consent form that will facilitate the use of biospecimens in open-ended future research as opposed to being study-specific.[172] Although not study-specific, the broad standardized consent form would have check-off boxes for special categories of research that an individual may not want to participate in "given the unique concerns they might raise for a significant segment of the public…."[173]

[48] As written, the ANPRM interconnects the concepts of broad and tiered consent, as it affords individuals the opportunity to consent to all unforeseen future research with their biospecimens and to refuse having their biospecimens used for special categories of research. Although attempting to strike an appropriate balance for the unforeseen future use of biospecimens by protecting human subjects' autonomy without impeding biomedical research, the ANPRM is imperfect in that the consent model

[170] *See* ANPRM, *supra* note 16, at 44,512.

[171] *See id.* at 44,519.

[172] *See id.*

[173] *Id.* at 44,519–20.

proposed facilitates stigmatization. The allowance of special categories facilitates the stigmatization of medical conditions that individuals are hesitant—if not reluctant—to provide consent for. Thus, implementation of the consent model proposed will impede biomedical research by (1) discouraging individuals from consenting to the use of their biospecimens for conditions identified as special categories, (2) decreasing studies seeking to characterize and identify treatments for stigmatized conditions, and (3) decreasing the number of investigators addressing stigmatized conditions.

[49] By identifying special categories of research in which individuals may want to refrain from, the proposed consent modifications are further stigmatizing conditions that certain members of the public may find objectionable. In doing so, it is reasonable to suggest that individuals may have a tendency to automatically decline consenting to research related to those special categories. Such a decision may be based upon imperfect or insufficient information in that an individual may believe that the federal government has conducted extensive, well-controlled, and demographically diverse studies to determine individuals' perspectives on what categories of research they find objectionable.[174] Likewise, an individual may suspect that the federal government has conducted analyses balancing the potential risks and benefits associated with the special categories of research and therefore decline to have their biospecimens used for research aligned with the special categories.

[50] Implementation of federal regulations requiring consent forms to identify special categories of research that a potential participant may find objectionable would be detrimental to the underlying purpose of the ANPRM, which is to improve individuals' autonomy. By identifying special categories of research, consent would not be informed by a disclosure of information related to the research that may be conducted or of its risks or benefits. Rather, individuals would be influenced by the

[174] It is unclear at this time how the federal government intends to determine whether research on a specific disease state should be classified as a special category.

federal government's identification that research befitting of special category designation may not be in their best interests to participate in. The ANPRM's consent model therefore may be construed as coercive in that the federal government's opinion as to what constitutes a special category would influence a person's decision to having their biospecimens used in unforeseen future research designated as special.

[51] Biomedical research focused on the identified special categories may also be impeded if the scope of the special categories is overly broad. If overly broad, the special categories would preclude individuals from allowing their biospecimens to be used for any research that would fall within that designated special category.[175] For example, if reproductive medicine was used as a special category, an individual would be unable to designate that they would not want their frozen human embryos used for creating a cell line as opposed to assessing developmental disorders or understanding predispositions to infertility. Thus, research in these areas would be impeded due to the breadth of the reproductive medicine special category.

[52] Additionally, if the special categories are overly broad, the ability to conduct correlative studies—which may identify the role of a specific gene, protein, or molecular mechanism in multiple and pathologically diverse conditions—may be impeded. Investigators seeking to understand whether there is a genetic correlate to chemotherapy induced infertility would be precluded from using any biospecimens of cancer patients that did not consent to their specimens being used for reproductive medicine research. Thus, by decreasing research participation in special categories the proposed consent model would decrease autonomy by hindering an individual's informed decision, further the stigmas associated with the identified special categories, and impede scientific advances to understand, treat, and ultimately de-stigmatize these conditions.

[175] *See*, Julie A. Burger, *What is Owed Participants in Biotechnology Research?*, 84 CHI.-KENT L. REV. 55, 70 (2009).

[53] As previously noted, identification of special categories will hinder biomedical innovation for stigmatized conditions classified as special by increasing the reluctance to consent to the use of biospecimens for future research. Thus, implementation of an interconnected broad-tiered consent model using special categories would decrease the number of biospecimens available for unforeseen future research. A lack of biospecimens would also impede biomedical research as investigators would not have an adequate and diverse supply of samples to use in addressing their research hypotheses. Due to a limited sample supply, investigators may choose to modify their research hypotheses addressing special categories. Alternatively, investigators may direct their efforts towards answering questions based on the availability of samples they can obtain (e.g., cancer-related diseases) as there will be a more robust sample population in which to conduct both small and large scale studies.

[54] The identification of special categories of research also changes the federal government's functionality from a regulatory body providing oversight for research involving human subjects to an advocacy organization. Here, the federal government is advocating that research focused on one type of disease (e.g., cancer) should evoke robust participation whereas research focused on special categories of disease (e.g., reproductive medicine) should not. As such, the implementation of an interconnected broad-tiered consent model that identifies special categories of research allows the federal government to dictate innovation by identifying which fields of research are most important and where resources should be directed.

III. PROPOSED CONSENT MODEL: BROAD CONSENT WITH THE OPTION TO BE RECONTACTED

[55] In determining whether there is a consent model that adequately addresses the concerns of research participants and investigators, the answer is seemingly "it depends." As noted above, the broad-tiered hybrid consent model proposed in the ANPRM would deter consent for future

research efforts in special categories. A consent model applicable to both respecting participant autonomy and facilitating medical research is one where an individual provides blanket consent to future unforeseen research with the option to be recontacted for specific categories of research.

[56] This proposed consent model protects an individual's autonomy by allowing them to make an informed choice about whether to participate in special categories of research. The participant's choice is informed by having the option to be recontacted if the use of their biospecimens would be integral to a particular area of research. The recontact option ensures that an individual is making an informed choice by understanding the specifics of the special category based studies their specimens would be used for. The option to be recontacted for special categories of research therefore provides for a sustained interaction to be developed with a biospecimen donor.

[57] To assess the utility of the broad consent model with the option to be recontacted (BCORED), this author provides an overview of how its implementation may be applicable in the context of reproductive medicine. As noted above, since the release of E.O. 13505[176] and its implementation by the NIH,[177] federal funding and scientific inquiry using hESC lines has increased. However, indecision by prospective donors as to the disposition of their frozen human embryos continues in part due to a lack of clear processes for making an informed decision.[178]

[58] Here, we envision a continuous consent process for the donation of human embryos for research purposes. The consent process would be

[176] *See* Executive Order, *supra* note 2.

[177] *See* NIH Guidelines, *supra* note 5.

[178] *See* Tasha Kalista et al., *Donation of Embryos For Human Development*, 8 CELL STEM CELL 360 (2011).

initiated annually as prospective donors are given disposition options for their embryos included with their annual storage bill from their IVF clinic or storage facility.[179] The timing of seeking informed consent is critical in the context of reproductive medicine. It is important that prospective donors make the decision to donate after deciding to no longer store their embryos.[180] Doing so protects the donors from undue influence or pressure to donate from overzealous clinicians, researchers, and institutions.[181] Further, it ensures that donations are made without any potential misconceptions about restrictions or benefits of care depending on the donor's disposition decision.[182]

[59] If interested in donating their embryos for research, donors would receive an informed consent packet. The informed consent packet must be consistent with federal regulations governing human subjects research and NIH guidelines regarding research with human embryos. The informed consent packet will be broad in that it allows the donor to consent to all unforeseen future research that their donated embryos may be used for. However, to be consistent with NIH and ASRM guidance consent forms would also include categories of research—including stigmatized research categories—that the embryos may be used for. These categories may include reproductive medicine—such as early human development, embryo quality, and improving IVF clinical outcomes—or the production of cell lines for research purposes. Included in the informed consent packet would also be information on the right of the donor to withdraw from the research. Following NIH guidelines, donors would be informed that they retain the right to withdraw consent to donate their embryo(s) until the time that the embryos were used to drive hESCs or until

[179] *See id.*

[180] *See* ASRM Ethics Comm., *supra* note 41, at 935.

[181] *Id.* at 938; *see also* NIH Guidelines, *supra* note 5.

[182] *See* NIH Guidelines, *supra* note 5.

information linking the identity of the donor with the embryo was no longer retained.[183]

[60] Contact information for biobank coordinators would also be included in the informed consent packet. The central function of the biobank coordinators would be to discuss the current research projects that the embryos may be used for, confirm an individual's understanding of the differences in the research categories, and confirm their intent to donate.[184] Following confirmation of the consent to donate, the biobank coordinators would also work with the donor's IVF clinic or storage facility to transfer embryos.[185]

[61] Although this structure of informed consent is similar to the broad-tiered consent hybrid model proposed in the ANPRM, the consent model noted above is caveated in that it would also allow for donors to be recontacted. Recontact permits research related issues—such as future study—to be discussed with individuals on an ongoing basis.[186] Developing a sustained interaction with individuals is critical to ensuring that they are making an informed decision about the use of their donated embryos and/or other biospecimens, specifically for research on stigmatized conditions. The ability of donors to make an informed decision under this framework will be facilitated by their sustained interaction with the biobank coordinators who can provide more detailed information (e.g., for stigmatized research) about the ongoing uses about their embryos.

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[183] *See id.*

[184] *See* Kalista, *supra* note 178, at 360–61.

[185] *See id.* at 361.

[186] Justin Lowenthal et al., *Specimen Collection for Induced Pluripotent Stem Cell Research: Harmonizing the Approach to Informed Consent*, 1 STEM CELLS TRANSLATIONAL MED. 409, 414 (2012).

[62] Protecting individual's autonomy without impeding the progress of biomedical research is essential to any informed consent model. Implementation of the BCORED model assists with this goal, especially as it relates to research on stigmatized diseases. As noted above, the broad-tiered consent hybrid model proposed in the ANPRM facilitates stigmatization by allowing an individual to opt-out of any and all special categories of research that their biospecimens may be used for. As an alternative, the BCORED model proposed herein may increase the willingness of individuals to have their biospecimens used for stigmatized conditions. Here, a donor has a better understanding of how and why their embryos or biospecimens will be used due to the sustained interaction with the biobank coordinator.

[63] The sustained interaction gained from the BCORED model both increases communication to inform donors about the research they will be contributing to and creates openness within the research enterprise.[187] Such openness may assist in increasing donor willingness to participate in research they may have objected to previously due to imperfect or insufficient information. Increases in participation are also likely to attract investigators to study stigmatized conditions due to the increase in the number of samples available to address specific research hypotheses and conduct correlative studies. Thus, the BCORED model would increase autonomy by supporting a donor's informed decision, increase research participation for stigmatized conditions, and facilitate investigations on stigmatized conditions due to a more robust sampling of biospecimens in which to test research hypotheses.

[64] Importantly, the BCORED model is consistent with empirical research studies focused on potential donors' perspectives. Empirical research suggests that donors would prefer to exert some level of control over whether their biospecimens can be used in unforeseen future research, with the majority indicating that a broad consent model

[187] *See* Rosario Isasi et al., *Sustained Interaction: The New Normal for Stem Cell Repositories?*, 6 REGEN. MED. 783, 783 (2011).

adequately addresses that preference. However, the option to be recontacted assists in overcoming a significant challenge to informed consent related to embryo disposition: that a potential donor's attitude about their embryos changes overtime.[188] By allowing for the option to be recontacted, donors are able to make an informed decision about which additional studies—if any—to participate in upon recontact, a decision which may have changed overtime.

[65] This author acknowledges that his recommendations for implementation of a consent model that allows donors to be recontacted to support a sustained interaction have previously met criticism. Although recontacting donors has been considered impractical under a study-specific consent model due to the costs and logistical roadblocks associated with recontact,[189] the BCORED model may help quash those concerns. The BCORED consent model uses biobank coordinators to maintain the sustained interaction with donors. The biobank coordinators would be responsible for recontacting donors, explaining details of the research, obtaining informed consent and withdrawal requests, and answering any questions or concerns that donors may have. As these tasks do not align with the duties of the investigator, there is no impediment to his or her research due to administrative burden.

[66] Likewise, implementation of the BCORED model does not substantially increase research costs. Research costs under the BCORED model are mitigated by the use of a biobank coordinator. Salary support for the biobank coordinator would be paid by the biobank at no additional cost to the investigator. The investigator would only be required to pay for

[188] *See* Lyerly, *supra* note 45, at 650 (citing Robert Nachtigall et al., *How Couples Who Have Undergone in Vitro Fertilization Decide What To Do with Surplus Frozen Embryos*, 92 FERTIL. STERIL. 2094–96 (2009)); CR Newtown et al., *Changes in Patient Preferences in the Disposal of Cryopreserved Embryos*, 22 HUM. REPROD. 3124,25 (2007).

[189] *See* ANPRM, *supra* note 16 at 44,524.

the use of the biobank (i.e., to obtain informed consent and acquire biospecimens) which would be documented in their federally funded grant or contract. Even if the biobank requires salary support for biobank coordinators to be supplemented by the investigators, direct research costs would not be substantially impacted as the use of biobank coordinators would obviate the need for on-site research coordinators to obtain informed consent or recontact prospective donors.

IV. CONCLUSION

[67] Informed consent is central to the conduct of biomedical research involving human subjects. It is critical that potential research participants be presented with sufficient information to make an informed decision about whether to participate in both primary and unforeseen future research studies. However, there is a concern as how to appropriately balance an individual's autonomy as related to the unforeseen future use of their biospecimens with the advances in biomedical research. Implementation of the BCORED model improves upon the current federal regulations governing informed consent in that it allows individuals to give broad consent to any and all research or to be recontacted to discuss specific categories of research that may be stigmatizing. In doing so, the BCORED model ensures that an individual's autonomy is protected by affording the opportunity to make an informed decision about the future use of their biospecimens. Likewise, the BCORED model does not impede biomedical research as it uses a third party intermediary for recontact and may result in a more robust, heterogeneous sample of biospecimens to find "the cure" for diseases, including those that routinely elicit stigmatization.