HHS Public Access

Author manuscript

Hastings Cent Rep. Author manuscript; available in PMC 2023 February 09.

Published in final edited form as:

Hastings Cent Rep. 2022 November ; 52(Suppl 2): S2–S23. doi:10.1002/hast.1427.

Clarifying the Ethics and Oversight of Chimeric Research

Josephine Johnston,
The Hastings Center

Insoo Hyun,
Case Western Reserve University

Carolyn P. Neuhaus,
The Hastings Center

Karen J. Maschke,
The Hastings Center

Patricia Marshall,
Case Western Reserve University

Kaitlynn P. Craig,
Case Western Reserve University

Margaret M. Matthews,
The Hastings Center

Kara Drolet,
Oregon Health & Science University

Henry T. Greely,
Stanford University

Lori R. Hill,
MD Anderson Cancer Center

Amy Hinterberger,
King's College London

Elisa A. Hurley,
PRIM&R

Robert Kesterson,
University of Alabama at Birmingham

Jonathan Kimmelman,
McGill University

Nancy M. P. King,
Wake Forest University School of Medicine

Melissa J. Lopes,
ESCRO Committee

P. Pearl O'Rourke,

Harvard Medical School

Brendan Parent,
NYU Grossman School of Medicine

Steven Peckman,
University of California, Los Angeles

Monika Piotrowska,
SUNY at Albany

May Schwarz,
The Salk Institute for Biological Studies

Jeff Sebo,
New York University

Chris Stodgell,
University of Rochester

Robert Streiffer,
University of Wisconsin-Madison

Amy Wilkerson
The Rockefeller University

Introduction

For decades, researchers have inserted different types of human cells into nonhuman animals at various stages of development.[1] Sometimes the goal is to create a model of human biology or human disease, as for example, when scientists insert human cancer cells into adult nonhuman animals before testing the effectiveness of a new cancer drug. Sometimes the goal is to study how human tissues and organs develop. This might be done by transferring different types of human stem cells into nonhuman animal embryos and culturing those embryos in the lab or gestating them for a short time in nonhuman surrogates. These cell transplantation studies—and others like them—have helped scientists learn how human diseases develop, how human cells behave in a living environment, and how human tissues and organs form. Research with nonhuman animals containing human cells has also led to the development of islet cell transplantation for Type 1 diabetes, a promising new investigational intervention.[2] Other chimeric studies, such as alteration of a pig fetus so that it might develop human organs, like a kidney or a heart, aim to one day alleviate the critical shortage of human organs for transplantation.[3]

Many scientists use the term “chimera” to describe nonhuman animals and nonhuman animal embryos that contain human cells (as explained below, we choose not to use this specific term, at least not without qualifiers). In the scientific literature, the term broadly applies to all organisms that carry cell populations derived from two or more genetically distinct sources. The research may be in vitro (e.g., studies of chimeric embryos in a Petri dish), or in vivo (e.g., studies of chimeric embryos or chimeric fetuses that are gestated in live female animals, or studies of postnatal chimeric animals). The transplanted cells

may come from another individual of the same species—in scientific research, one of the most commonly used chimeric animals are mice with cells from other mice. Or the transplanted cells may come from a different species, as is the case in human-nonhuman chimeric research, which commonly involves the transfer of human cells into nonhuman animals such as laboratory rats. These human-nonhuman chimeric studies are sometimes labeled controversial or morally troubling and have been the focus of ethics and policy attention. For almost as long as scientists have conducted human-nonhuman animal chimeric research there has been debate about whether such scientific work should take place, and if it does, how best to respond to the ethical and policy issues it raises.[4] Although regulatory bodies, like the Food and Drug Administration in the United States, and similar authorities internationally, require researchers to test stem cell-based biologics in animal models proceeding to human trials, these translational research requirements are not enough to quell some people's ethical concerns. Scholars in bioethics, philosophy, religious studies, and other academic fields, as well as scientists, journalists, policymakers, and religious and animal rights organizations, have discussed and debated various ethical and governance questions related to this research. These questions include whether the moral status of nonhuman animals is altered by the insertion of human cells,[5] whether it is morally appropriate to cross species boundaries in this way,[6] whether it is acceptable to patent these new kinds of nonhuman animals,[7] and whether human-nonhuman chimeric animal studies should be subject to additional prohibitions or oversight beyond those generally imposed on research with human cells and research with nonhuman animals.[8]

In the U.S. and several other countries, national bioethics advisory committees and other advisory bodies have published reports addressing some of these ethical and policy questions. Most reports have focused on embryonic and other kinds of stem cell research, addressing stem cell-based chimeric studies among a range of other issues. In the U.S., the most influential of these guidelines have come from the U.S. National Academies (now the National Academies of Sciences, Engineering, and Medicine; NASEM) first issued in 2005[9] and last updated in 2010,[10] and from an international scientific society called the International Society for Stem Cell Research (ISSCR), first issued in 2006[11] and last updated in 2021.[12] In 2021, the NASEM Committee on Science, Technology, and Law issued a report that includes the committee's consensus findings about the science, ethics, and governance of human neural organoids, transplants, and chimeras.[13] In addition, funders of research have sometimes developed policies touching on chimeric studies. The U.S. National Institutes of Health (NIH) currently will not fund certain types of chimeric research, a policy that has led some U.S.-based researchers to seek funding from alternative sources, including private foundations.[14]

In these reports and recommendations, some types of chimeric study are singled out for additional oversight, and some specific activities—such as mating of nonhuman chimeric animals—are prohibited. The ethical bases for these chimeric research-related prohibitions and restrictions are sometimes unclear, making it difficult to assess and reconcile governance and oversight or know how to adapt to changing public attitudes or changing science. In addition, oversight approaches are fragmented, and specific rules or guidelines can be difficult for researchers and oversight committees to operationalize.

In response to these uncertainties and to an absence of empirical data about the perspectives, insights, and experiences of scientists and oversight committees, researchers at The Hastings Center and Case Western Reserve University conducted an interdisciplinary research project to clarify the conceptual, ethical, and policy issues raised by chimeric research. Our research team conducted in-depth interviews with a sample of scientists and oversight committee stakeholders across the U.S.[15] We also analyzed the scientific literature and literature in bioethics and other fields, including academic articles and books as well as national and international reports, recommendations, guidelines, and surveys. We convened an expert Project Work Group [see Box 6] to discuss both theoretical and practical issues surrounding chimeric research in a series of Work Group workshops.

This Special Report, which comprises this article and six accompanying essays, presents the results of our conceptual, ethical, and oversight research. While we, the authors of this report, agree that there is value in disentangling and analyzing the ethical concerns associated with chimeric research, we are not in full agreement about their implications. In particular, we disagree about whether in vivo chimeric research should happen at all. In this report we do not take a stand on that issue one way or the other. Instead, we discuss how to understand, assess, and regulate this type of research as thoughtfully as possible to the extent that it does happen. That said, we do agree that one particular concern is key: the welfare of the nonhuman animals used in chimeric studies.

The Special Report adds value to the current national and international discussion about chimeric research by reorienting ethical analysis to place a greater emphasis on nonhuman animal welfare concerns and less emphasis on issues such as concerns about the “humanization” of nonhuman animals or taboos around crossing species boundaries. We also offer recommendations for improving governance and oversight of this diverse category of research. Our analyses and recommendations are developed for and within the U.S. context. Because many of the ethical and oversight issues we address here are being faced by other nations, we hope our work will be useful across national borders.

Beyond the substance of this Special Report, we also note that, in contrast to some other reports referenced above, this report’s authors were not appointed by a national government or a government body (although the project from which this report emerges was carried out under a federally funded grant) and do not represent the interests of scientists or any other particular stakeholders. Rather, we are a bioethics research team working in partnership with an interdisciplinary workgroup of scholars and oversight experts.

In this project, we focused on chimeric research that is *stem cell-based*, that is, research involving the transfer of human embryonic or induced pluripotent stem cells, or cells derived directly from them, into nonhuman animals or nonhuman animal embryos.[16] Although chimeric research can include the transfer of many other human cell types (e.g., cancer cells), we focused on stem-cell based chimeric studies for three reasons. First, the effect of transplanted stem cells on nonhuman animals or embryos is potentially more systemic but also more unpredictable than the effect of transplanting more specialized cells. Second, most, if not all, of the recent bioethics literature on chimeric research engages exclusively with stem cell varieties of this scientific work. Our analyses and recommendations are meant

to add to this rich body of literature. Third, the influential guidelines issued by professional scientific bodies such as the National Academies and the ISSCR solely concern chimeric research involving the transfer of human pluripotent and multipotent stem cells or their direct derivatives into nonhuman animals. In this project, we have endeavored to identify ways these stem cell guidelines could be better justified and made more operational to better support implementation by researchers and their institutions. Despite our focus on stem cell-based chimeric research, much of our analyses and recommendations will be relevant for non-stem cell-based studies.

This article is arranged in four main subsections following the foci of our project: a section on language, a section for each of the two main types of ethical issues (concern for nonhuman animals, concern about human dignity and integrity), and a fourth section addressing oversight and governance challenges.

Descriptive Language to Facilitate Ethical Clarity

> **Recommendation #1**:Scientists, bioethicists, journalists, and others writing about chimeric research should seek to use precise and accessible language that clarifies rather than obscures the ethical issues at stake. In particular, we discourage use of the nouns “chimera” and “humanization”.

Clear, accurate, and accessible language can promote understanding of research that raises conceptual and ethical concerns. Some of the language used in discussions about human-nonhuman chimeric research can be obscure or frightening, in particular the term “chimera,” which in Greek mythology refers to a fire-breathing monster. Language can also intentionally or unintentionally suggest or connote certain ethical concerns about or conclusions regarding the research, as is arguably the case with the term “humanization”. Terms that are obscure, frightening, ethically-laden, or overly broad can foreclose opportunities to understand the nature and outcomes of the work.

In this article, we have made decisions about various key terms in the human-nonhuman chimeric research debate that we hope others will consider adopting when discussing the science, ethics, and policy of this research:

- “Chimeric research,” or “chimeric nonhuman animal”, or “chimeric embryo” but not “chimera”: In contemporary biomedical science, the noun “chimera” describes an embryo or nonhuman animal created for research and carrying cell populations derived from two or more genetically distinct sources. Although often used in scientific publications, there are numerous problems with the term. Few nonscientists understand what it means. Its connotations are literally monstrous—media reports of human-nonhuman cell transfer research often describe or present images of monsters.[17] And it does not clearly differentiate between in vitro research (studies conducted with cells and embryos in a laboratory dish) and in vivo research (studies involving a living nonhuman animal). Indeed, the term obscures not just whether the research is in vitro or in vivo, but the type of nonhuman animals involved, thereby obscuring some of the most important ethical issues at stake. Some committees have recognized

this challenge but dealt with it by reserving the term chimera for specific study types.[18] Others have developed new terms such as “animals containing human materials.[19] We avoid the noun “chimera” altogether. Instead—and in recognition of the long-standing use of the term in the scientific literature—we use the adjective “chimeric” to signal research involving a mix of cell sources but where possible include details about the relevant in vivo or in vitro organism, such as “chimeric mouse embryo,” “chimeric pig fetus,” or “chimeric postnatal monkey.”

- “Nonhuman animals or embryos with human cells” but not “humanized” or “humanization”: In science, a “humanized” nonhuman animal has been modified to contain human genes, cells, tissues, or organs. The term indicates biological changes in the nonhuman animal. It is not intended to convey any specific changes in the nonhuman animal’s behavior or its moral status. Yet in ethics discussions, “humanized” can code for a set of distinct concerns about human dignity and human morality that, as discussed below, are contested. It is a mistake to absorb these ideas into seemingly neutral scientific terminology. We therefore avoid using the terms “humanized” or “humanization”, even though they do appear in the scientific and ethics literature, preferring instead descriptive terms explaining what has been or will be done in an experiment. If the term “humanized” must be used, we recommend that scientists and other relevant experts include clarificatory language. For example, instead of “the mouse was humanized” or “we created a humanized mouse,” one might say “human embryonic stem cells were added to the mouse’s brain/liver/bloodstream” or “in this study we created a mouse with X% human brain cells in the cerebellum.” Likewise, instead of voicing a moral concern such as “the nonhuman primate is humanized and therefore should not be used in research,” we encourage the more specific statement “the nonhuman primate’s enhanced capacity for cognition and self-awareness mean that it should not be used in research.” If the term “humanized” must be used, we recommend that scientists and other relevant experts include clarificatory language.
- “Human and nonhuman animals” rather than “humans and animals” to draw attention to the fact that we humans are also animals, a fact that can be obscured when the term “animal” exclusively refers to nonhumans.

Concern for Nonhuman Animals

Recommendation #2: Ethical and policy analysis as well as governance and oversight of chimeric research should focus on the welfare of any nonhuman animals involved in such studies. Animal welfare is a primary ethical issue and should be a focus of ethical and policy analysis as well as governance and oversight of this research.

Our underscoring of the crucial importance of nonhuman animal welfare may come as a surprise to readers familiar with the relevant ethics literature. As discussed below, much of the past ethical analyses of chimeric research has focused on issues associated with the

derivation and use of human stem cells, taboos over crossing species boundaries by mixing human cells with cells from nonhuman animals, concerns that chimeric animals will be "human like," and theoretical discussions of moral status, personhood, and human dignity when nonhuman animals contain human cells.[20] We address these issues below, but note here that placing them at the forefront of ethics and oversight recommendations for chimeric research risks ignoring one of the most ethically salient facts about these studies: namely, that chimeric research involves nonhuman animals with interests grounded in (at least) their sentience.[21]

Even the creation of chimeric embryos directly involves nonhuman animals: eggs and sperm are procured from these animals to create the embryos into which human stem cells are transferred. Chimeric embryos are also sometimes implanted in female nonhuman animals for gestation, whether until birth or for a shorter time before being surgically removed, all of which also directly involves a nonhuman animal. In light of the inescapable involvement of nonhuman animals in chimeric research, their interests should be a focal point of ethical analyses and governance.

We understand that welfare is an issue for all research with nonhuman animals, and that concerns for the welfare of animals in research is leading to the development of alternative approaches, including organoid systems and human-based assays. In many senses, chimeric studies are just another type of research with nonhuman animals. Yet chimeric studies raise the additional possibility of unique or novel harms resulting from the insertion and development of human stem cells in nonhuman animals, particularly when those cells develop in the brain or central nervous system. Chimeric studies are also an area of growing research interest, raising the possibility that they will result in more nonhuman animals being used in research. And because much ethics analysis of chimeric research has focused on issues related to human dignity and integrity, the welfare of nonhuman animals in these studies risks being overlooked.

We try to remain as agnostic as possible in this article about the philosophical basis of duties that humans owe to nonhuman animals. Yet we take as settled that nonhuman animals occupy a moral status that sets limits on how and the extent to which humans can use them in research.[22] With respect to nonhuman animals proposed for use in chimeric research (including mice and other rodents, pigs, and primates), we endorse R.G. Frey's assertion that a nonhuman animal's life is:

An unfolding series of experiences, that, depending on their quality, can make that creature's life go well or badly. Such a creature has a welfare that can be positively and negatively affected, depending on what we do to it, and with a welfare that can be enhanced and diminished.[23]

Because nonhuman animal welfare is a matter of moral significance, using them in virtually any kind of research raises ethical questions. Breeding, rearing, and using animals in research influences their experiences and the quality of those experiences, thereby imposing enormous responsibility on the scientific teams and institutions involved with such research. It is clearly unethical to subject nonhuman animals to harms caused by

laboratory confinement and scientific experimentation when there is no or merely trivial anticipated knowledge produced by doing so, as well as when the anticipated benefit is very unlikely to be obtained. But even in studies likely to produce valuable knowledge, there is a widely accepted ethical obligation to abide by the three Rs—replacement, reduction, and refinement—as proposed in Russell and Burch's influential book *The Principles of Humane Experimental Technique*.[24] The three Rs and other general principles for nonhuman animal research clearly apply to chimeric research, but it is also important to highlight and incorporate the welfare concerns about nonhuman animals explicitly into the governance and oversight of chimeric research. We are not suggesting that animal welfare is currently ignored in chimeric research—indeed we learned from some workgroup members that concerns over the appropriate use of animals in biomedical research animate funding discussions and, in their experience, can contribute to decisions to not fund specific research proposals. However, we are urging researchers, ethicists, policy makers and others to keep animal welfare front and center.

> **Recommendation #3:** Scientists, scholars, and other stakeholders should together undertake a focused analysis of what it means for chimeric studies to have a sufficiently strong scientific justification for the proposed use of nonhuman animals.

For almost a century, research that advances understanding of human biology and seeks to improve our ability to prevent and treat human disease has been a national priority in the U.S. and in many other nations. Governments and other funders devote billions of dollars each year to biomedical research, institutions showcase biomedical science in their missions and budgets, and hundreds of thousands of individuals voluntarily participate in studies, donate their own funds to research, and devote their careers to its advancement. Justifications for this substantial commitment of talent and resources include that the knowledge produced through biomedical research leads to new diagnostics and treatments, drives economic growth, and in some cases can reduce healthcare costs. These instrumental justifications are premised on the belief that humans are intrinsically morally significant, and perhaps even that the prevention and relief of suffering in other humans is among our highest moral callings.

Whether instrumentally or intrinsically grounded, the case for biomedical research focuses on the interests and well-being of humans. As important as those interests are, they are not absolute, and the methods used in the production of new biomedical knowledge must be subject to some constraints. Just as research with humans is subject to limitations and oversight requirements developed in the wake of ethically indefensible harms and injustices, so too is research with nonhuman animals. These limitations vary depending on the goals of the study, the type of nonhuman animal involved, and the particular harms they may be subject to. Some constraints are absolute, but others are weighted against the potential benefits of the research, a calculation that generally prefers the interests of humans.

Virtually all chimeric research has welfare implications for nonhuman animals yet promises to advance knowledge that will primarily be relevant to human health and well-being. In this way, chimeric studies are much like other kinds of research with nonhuman animals. It is ditherefore important to be able to assess the strength of the claim that a particular chimeric

study addresses important questions, is well-designed, and is necessary to answer those questions—that it is "scientifically justified." The 2021 ISSCR Guidelines for Stem Cell Research and Clinical Translation state at several points that research, including chimeric studies, should be "well justified."[25] What well or scientifically justified means for chimeric studies, whether in theory or in practice, is not explained.

This omission is not unusual; "scientifically justified" is seldom defined—in chimeric research or other research—and approaches for evaluating it in studies that explicitly seek to model aspects of human biology in nonhuman animals have not been identified. But it is a pressing question in an area of research such as chimeric research where increasing numbers of studies with nonhuman animals are being planned and undertaken, where novel harms are possible, and where the welfare of nonhuman animals has not been widely acknowledged to be a primary ethical issue. Leaving the term vague not only makes assessment and oversight challenging, but it also invites assumption of scientific merit. Indeed, ethical analyses of chimeric research generally operate from the assumption that rigorous scientific review and justification has already been established, without diving deeper into what it takes to meet this bar.[26] While many chimeric studies undergo peer review when they are submitted for funding, which is generally before they are presented to oversight bodies, not all studies will have done so.

Questions about the meaning of "scientifically justified" and how to assess the strength of the scientific justification are not unique to chimeric research—they are important questions for all research with nonhuman animals. Indeed in nonhuman animal research generally, concerns have been raised about whether nonhuman animals are less robust models of human biology than hoped, and that studies with nonhuman animals may not generate the kind or quality or degree of knowledge claimed, whether because the studies rest on faulty scientific or philosophical premises, have methodological flaws, or permit bias.[27] Chimeric studies are a response to at least the first of these concerns because they involve nonhuman animals with human cells, tissues, or possibly one day organs; nonetheless, as with all models of human biology the scientific benefit of research with chimeric embryos, fetuses and/or post-natal animals should not be taken for granted.

Identifying and describing the components of a strong scientific justification for chimeric research is a complex undertaking requiring input from a broad range of scientific and other experts, a process that would ideally involve other stakeholders as well. This undertaking involves several outstanding theoretical and process questions about scientific justifications, how they ought to be assessed, and by whom. Examples of theoretical questions include whether the distinction between so-called basic and translational research is relevant when assessing a study's scientific justification,[28] and whether scientific justifications ought to include an assessment of the tangible benefits of a particular line of biomedical research (e.g., the development of treatments or other interventions) or be limited to an assessment of the likelihood of knowledge production from a particular experiment.[29] Examples of process questions includes who ought to be involved in the assessment of scientific justification and how to balance scientific justification against other considerations that count for and against a particular experiment. For example, should a study that is assessed to be scientifically justified and even necessary to advance human health be subject to any other ethical

constraints? Analyses of the scientific justification of chimeric research may be enriched by critiques of scientists' reliance on nonhuman models more generally. It is our understanding that the ISSCR is currently exploring the meaning and assessment of scientifically justified in the context of stem cell research, an undertaking that we hope other interdisciplinary groups will also engage in.

> **Recommendation #4:** *Researchers conducting chimeric studies with nonhuman animals should systematically assess the behavior of their nonhuman animal subjects so that novel changes can be detected, monitored, and reported, including behavioral changes that might indicate novel or unexpected forms of pain, suffering, or lack of flourishing potentially caused by the presence of human cells, especially in the nonhuman animal's brain or central nervous system*.

As stated above, **many of the familiar concerns about conducting research with nonhuman animals are relevant to** chimeric **research**, chief among them is the welfare of the nonhuman animals, especially when that they have been altered to model human disease. In chimeric research, a particular concern is that the nonhuman animals might experience novel, unexpected, difficult to detect, or more acute discomfort, pain, distress, or stress resulting specifically from the presence of human cells. The alteration of basic cellular, chemical, or other physiologic processes might be painful, possibly in novel ways. This concern is especially significant now, because chimeric studies modeling human diseases, especially neurological conditions are still in their early days.

Chimeric research that involves the creation of models of psychiatric disorders in nonhuman animals (e.g., autism, depression, or schizophrenia) may rely on behavioral endpoints (e.g., antisocial behavior or self-harm) that cannot be medicated without undermining study design to validate models.[30] Yet those same behaviors may indicate stress, distress, or suffering. Do nonhuman animals involved in chimeric research experience these behaviors as *more* distressing than control conspecifics exhibiting similar behaviors? Control conspecifics may need to include *both* members of the same species, bred and reared in the lab and not used in disease modeling *and, when possible*, members of the same species with psychiatric illnesses induced in other ways (e.g., through genetic modification, chemical induction, or behavioral methods).

It is unknown whether existing methods for assessing welfare, which generally involve monitoring the behavior of nonhuman animals such as grooming habits, socialization, and eating, will be sufficient for detecting and assessing the welfare impact of the presence of human stem cells or their derivatives in nonhuman animals, especially human neural cells. Currently, the focus in ethics guidance is on the intended location of the human cells and the extent to which they engraft (sometimes expressed as the percentage of human cells in the nonhuman animal, which have thus far remained quite low). Because a large number of nonhuman animals could be involved in the development of chimeric animals serving as human disease models, researchers and their institutions should be equipped to look beyond percentage of engraftment and recognize and manage both familiar and novel signs and indicators of pain and discomfort at every step of the process.

Identifying any potential novel welfare issues may be difficult in practice. We learned in our interviews and from the project's Work Group members that some institutions do employ a designated staff person who has expertise regarding the behavior of nonhuman animals (their professional title might be a welfarist, behaviorist, or ethologist) to augment the expertise of a veterinarian who is typically a key member of the nonhuman animal research program. Moreover, not just the veterinarians, but also the veterinarian technicians, animal husbandry staff and other members of the research groups working with the animals should be involved. While the behaviorist can provide treatment plans, enrichment, etc. to enrich the life of the chimeric animal, or help prevent aberrant behaviors, the research staff working with the chimeric animals on a daily basis will be the ones who will notice if the changes (if any) in behavior are noticed. Thus, it is the collaborative effort of all that helps to notice and provide the necessary support.

It is currently unclear whether research institutions provide such expertise as a standard part of their nonhuman animal research programs, or whether researchers are able to obtain funding for inclusion of such expertise through their federal or private funding awards.[31] Experts in the behavior of nonhuman animals could play an important role in the identification of novel changes, including by creating a catalogue of behaviors they observe before and after they introduce human stem cells into nonhuman animals, so that changes in behavior or capacity can be more easily noted, quantified, and compared across research laboratories conducting similar types of studies. These experts could also develop cross-institutional standards for the welfare of the nonhuman animals used in chimeric studies, possibly developing their own literature on the topic. Funders and research institutions will need to support this additional work.

> **Recommendation #5:** *Bioethicists, journalists, and others writing about chimeric research should contextualize chimeric studies within ongoing debates in ethics, science, law, and society about the moral and legal status of nonhuman animals and the morality of using them in research. Developments in these debates may impact chimeric research, and vice versa*.

Often, discussions of the ethics of chimeric research focus on a narrow set of issues specific to the moral acceptability of research with human embryos, emphasizing links to the embryonic stem cell debate. Or discussions focus on the morality of mixing human and nonhuman cells, emphasizing links to debates about crossing species boundaries. These discussions may not differentiate between in vitro studies involving nonhuman embryos and in vivo studies involving post-natal nonhuman animals (more on these specific concerns below). In line with our recommendation 2, analyses and conversations can be enriched by acknowledging that chimeric research is first and foremost a form of nonhuman animal research. It is therefore part of broader debates and concerns about the use of nonhuman animals in scientific research. It is also part of ongoing debates, legal challenges, and societal discussions regarding the moral and legal status of certain nonhuman animals. These debates are in flux and may evolve in ways that significantly impact chimeric studies.

For example, debates about the moral and legal status of nonhuman animals used in chimeric research, especially nonhuman primates, should be informed by research and debates in the early twenty-first century that led the NIH, the world's largest funder of biomedical

research, to end its funding support of the use of chimpanzees in invasive research in 2015.[32] The same research and debates informed arguments presented in a legal case that unsuccessfully sought a writ of habeas corpus on behalf of two captive chimpanzees, attempting to recognize the legal personhood and right to bodily liberty of these two nonhumans.[33] While chimpanzees are no longer used in U.S. research, other nonhuman primates such as rhesus macaques are still used and in fact were critical animal models in research leading to the development of COVID-19 vaccines, for example.[34] Shifts in thinking about the moral and legal status of nonhuman primates in contexts outside chimeric research will almost certainly limit or otherwise impact chimeric studies.

Indeed, changes in public attitudes about the use of nonhuman animals in research in general may well impact views of chimeric research specifically. As scientists learn more about the complexity of nonhuman animals' lives and cognition, a moral hierarchy with humans at the top, alone entitled to certain moral and legal rights or protections is arguably untenable. Some bioethicists question the idea that research involving human subjects should fall under an entirely different moral and legal framework than research involving nonhuman animal subjects.[35] These questions are not felt solely by those opposed to animal research. Several scientists interviewed for this project noted that while they were not too worried about the overall ethics of the specific chimeric research they were involved in or its impact on nonhuman animals, discussion of the use and welfare of nonhuman animals in chimeric studies was an occasion for more thoughtful consideration generally about the balance of benefits and risks in research with nonhuman animals.[36] We take this observation as a sign that at least some stakeholders view chimeric research as an opportunity to further engage with ongoing discussion of the use of nonhuman animals in research.

Finally, we note that the connection between chimeric studies and broader animal rights debates might flow in the other direction. It is not difficult to imagine nonhuman primates involved in chimeric research, especially studies where human neurological cells are introduced, becoming case studies in larger debates about the moral and legal rights of nonhuman animals.

Respect for Humans and Concerns about Human Dignity

> **Recommendation #6:** *Opposition to chimeric research based on concerns about the use of human embryonic or other stem cells in such research, or about human integrity and dignity, should not warrant blanket prohibitions on chimeric research. Nevertheless, respect for the individuals who hold those views may motivate governance approaches that empower people to decide in an informed way whether to donate their cells to such studies.*

We focused above on concerns about the welfare of nonhuman animals involved in chimeric research, noting that such concerns deserve significant attention in ethics and policy addressing chimeric research. Here, we describe concerns about what chimeric research might mean for human dignity and human integrity and propose ways to address these concerns. We focus on two broad categories of human-centric concerns regarding chimeric research.

Public opinion surveys and polls[37] (and our preliminary analysis of public comments submitted to the NIH) show that some people are opposed to chimeric research due to their personal moral commitments regarding research that involves the use of human embryonic stem cells or their derivatives (and therefore is implicated in the destruction of human embryos for research). These same opinion surveys and polls (and our preliminary analysis of public comments submitted to the NIH) also reveal concerns about chimeric studies grounded in religious or cultural commitments to not crossing species boundaries, particularly the boundary between human and nonhuman animals. People with either or both of these beliefs may complain that chimeric research, especially when it uses their cells and perhaps also when it is undertaken using public funds, contravenes their beliefs. A commitment to respecting the beliefs of fellow citizens might justify imposition of some limits on chimeric research.

Human embryonic stem cell research has been controversial since at least the late 1990s when pluripotent stem cells were first derived from human embryos.[38] Opposition is most often grounded in concern for the human embryos that are destroyed in the derivation process, which some people see as full human beings or as entities whose moral standing is at least significant enough to obviate their use in research.[39] Arguments for and against embryonic stem cell research were publicly debated in the early 2000s, especially after President George W. Bush acted to significantly limit federal funding for the research. While public opinion polls continue to show that a majority of the public support the research,[40] opposition has remained and extends to chimeric research that uses embryonic stem cells or their derivates. The embryonic stem cell debate has been widely covered in the ethics literature—here we simply note that it informs some people's opposition to chimeric research.

Much of the bioethics literature, as well as research guidelines, proposed federal legislation, and proposed and enacted state laws regarding chimeric research, which explicitly or implicitly suggest that the integrity and moral standing (sometimes called "dignity") of humans is implicated when human cells are transferred into nonhuman animal embryos or post-natal nonhuman animals.[41] Guidelines direct specific attention to research that could result in changes to nonhuman animals so that they appear more "human-like," or to their brains so that they have enhanced or more human-like cognition.[42] The rationale for focusing on these kinds of potential changes in nonhuman animals—rather than or in addition to changes that increase pain in or otherwise decrease the welfare of nonhuman animals—is not generally directly spelled out, beyond noting that this kind of research can be particularly "controversial." But where the issue is not grounded in concern for the nonhuman animals involved, it may be that this kind of research is thought to offend some or all humans.

According to the strongest version of this concern, humans and nonhuman animals are and should remain separate. Mixing the two transgresses the biological boundary between "us" and "them", which may in turn confuse the moral status of the resulting nonhuman animal and also, by implication, of all humans.[43] This concern about blurring the boundaries between humans and nonhumans may draw on religious teachings, including a belief that humans were divinely created as separate from and superior to nonhuman animals.

The concern could also have a secular framing, pointing to the specific cognitive or communicative capacities of humans, or to the importance of maintaining a number of long-standing human practices, such as the farming and eating of nonhuman animals, that depend on the view that humans are morally distinct from nonhuman animals.[44] Mixing human cells with cells of nonhuman animal embryos or inserting human cells into post-natal nonhuman animals may be seen as blurring this boundary and thereby undermining or destabilizing a moral order that places human beings above nonhuman animals.

Critiques of the crossing species boundaries concern point out that species divisions are somewhat of a fiction scientifically.[45] Species are not fixed, but change as a result of evolutionary processes, nor are they clearly distinct from each other, as studies of the evolution and comingling of prehistoric humans have shown. Furthermore, humans and nonhuman primates are actually very similar biologically—human DNA is on average 99% identical to the DNA of chimpanzees and bonobos.[46] Humans are on a continuum with and connected to nonhuman animals. Critics may also argue that a history of domination of nonhuman animals does not prove that humans *ought* to maintain that dominion.[47]

The two broad human-centric concerns described here are difficult to adjudicate and may be impossible to reconcile (it is easy to see how someone deeply opposed to crossing species boundaries or the use of human embryos in research would reject a chimeric study involving human embryonic stem cells, no matter how strong the scientific justification or urgent the medical need it seeks to address). The authors of this report are not of one mind on all issues raised here. However, we have broad if not unanimous agreement that concerns about human embryos, as well as human integrity or human dignity, should not foreclose chimeric research.

That said, we recognize that it can be both morally important and politically necessary to develop policy and practice mechanisms that show respect for individuals who oppose chimeric research for these or other reasons. One important way of showing that respect may be to ensure that people who are opposed to this research are not directly involved in it, a strategy narrowly achieved by requiring that the human cells used in chimeric research were obtained with informed consent to their use in these kinds of studies.

Recommendations or guidelines requiring informed consent from the donors of embryos that will be used to derive human embryonic stem cells (hESCs) and of cells used in chimeric research seek to ensure that people who are opposed to this kind of research do not contribute their own biological material to it.[48] This strategy has been comprehensively addressed by other commentators and in various reports, recommendations, and guidelines.[49] We do note, however, two particularly tricky issues attending it: one regarding how specific that consent must be (should the consent be for the particular chimeric study, for chimeric research in general, or for a broader category of cell-based research?) and the other regarding whether that consent must come from all cell donors, including gamete donors involved in the creation of human embryos from which cells are extracted and then used in the study. While we support commitments to informed consent and see them as an important and powerful way to recognize an individual's opposition to chimeric (and related kinds of) research, we note that it can often be quite

difficult for researchers and their institutions to make good on the most demanding of these recommendations. We therefore support the use of consent forms that include general statements about future chimeric research (e.g., “cells or products may be transplanted to animals”) and requirements for obtaining consent from cell and embryo donors (but not necessarily any gamete donors involved in creating those embryos).

Governance and Oversight

Most scientific research is subject to some kind of governance—that is, to structures and processes that shape its development and conduct. These structures and processes include peer review of many research proposals and publications, ethics review of research with human and nonhuman animals, and the requirement for disclosure and management of financial interests. Where the goals or methods of a particular type of research are ethically complex, governance seeks to address those issues. Sometimes a stronger justification is required for certain studies. Research with children, for instance, is subject to more exacting risk-benefit calculations than research with adults. Sometimes additional oversight or monitoring is imposed. Studies involving investigators with a financial interest may be subject to independent monitoring or other conditions.[50] Sometimes limits are placed on which kinds of research are eligible for federal and/or state funding or whether the studies can take place at all. In several countries, research with human embryos cannot proceed beyond 14 consecutive days of development,[51] and in the U.S. research in which human embryos are harmed or destroyed is not eligible for federal funding.[52] Ideally, science governance directly addresses specified issues of concern, promotes accountability, and provides clarity and stability. It may also need to be responsive to the evolving nature of many scientific, ethical, or social contexts, meaning that good science governance can involve periodic reassessment to ensure that core principles or standards can still be met given new scientific developments or changes in how oversight is managed.

In chimeric research, U.S. governance frameworks and oversight mechanisms suffer from several limitations or challenges. In particular, the ethical rationales for governance in general and various rules and prohibitions in particular are not adequately identified and explained. Oversight can be fragmented. More than one oversight body or committee often addresses related sets of ethical concerns without clear ways to reconcile decisions. In addition, guidelines and funding policies may differ regarding the kinds of research that may be conducted, and the types of oversight required [see Box 2]. To address these limitations, we offer four recommendations aimed at improving governance and oversight. Although our analysis and recommendations are U.S.-centric, we hope that aspects of them will be helpful to regulators, researchers, and institutional leaders in other jurisdictions.

> **Recommendation #7:** *Within institutions, oversight committees that review chimeric studies should establish channels of communication and consider sharing expertise, perhaps by sharing members and/or staff. In addition, procedures for communication between committees should be developed so that committees can consult each other on matters of overlapping interest. At the institutional level, institutions should have mechanisms for tracking research portfolios involving chimeric research so that they can routinely assess the challenges posed by this*

research as well as any gaps in oversight. Institutions can then proactively decide whether these gaps are acceptable, whether existing oversight committees should assume responsibility, or whether a new process/committee is needed.

The three governance frameworks described in Box 2—focused on research with nonhuman animals, human subjects, and embryonic stem cells—all shape the conduct of chimeric research in the U.S. Those experienced in research with human embryos and hESCs will already be familiar with the challenges of managing one set of rules for federally funded research and another for research with nonfederal funds. However, the existence of two sets of guidelines for hESC research—especially when one set is regularly updated (the ISSCR guidelines) and the other is not (the National Academies' guidelines received their final update in 2010)—leaves oversight committees in a particularly challenging position when reviewing studies that are permissible under one but not both sets of guidelines, a challenge that has only grown as the ISSCR guidelines have been expanded to cover broader categories of research and relaxed to allow for review of research that it previously deemed impermissible. The result is that research institutions, researchers, and oversight committees are navigating a rather complex governance picture.

Variability also exists in how U.S. research institutions translate these guidelines into oversight of chimeric research. While all institutions will require review by Institutional Animal Care and Use Committees (IACUCs) and institutional review boards (IRBs) when required by law, many also require institutional approval for chimeric research if it involves hESCs, human induced pluripotent stem cells (hiPSCs), and at some institutions, human embryos. Institutions typically ask researchers to seek that approval from a standing specialized review committee—often called an "Embryonic Stem Cell Research Oversight (ESCRO) committee." However, some institutions (e.g., Oregon Health & Science University) use an ad hoc committee or institutional official to review these studies, sometimes in conjunction with the IACUC or IRB. Depending on an institution's oversight approach, some chimeric research might not be reviewed by any committee, or it might be reviewed for certain issues (e.g., nonhuman animal welfare) but not others (e.g., donor consent to the cell transfer use of human embryonic or induced pluripotent stem cells). Although there is no requirement for committees to work together, even when they are reviewing the same proposed study, some authors of this report have experienced institutional oversight that is collaborative across different domains, e.g., IACUCs, ESCRO committees, and IRBs interacting when they need input about specific studies. To encourage and facilitate this kind of interaction, the chair or other member of an IACUC could also be a member of that institution's ESCRO committee.

Because guidelines can vary in substance, oversight committees (as well as journals, funders, and other actors in this space) may sometimes choose *which* set of guidelines to follow and when to diverge from them (guidelines being recommendations not regulations). This choice may not be transparent—committees do not typically publicly report when they choose not to follow a particular guideline or publicly explain how they reconcile contradictory guidance. As also shown above, regarding some issues—such as when to permit studies in which human stem cells (or other human cells) are introduced to the brains of nonhuman animals—very little guidance is available. For example, there are no

clear guidelines for assessing specific changes in behavior in a nonhuman animal containing human stem cells that might raise ethical concerns. Committees currently have little choice but to employ a "we'll know it when we see it" approach to line drawing, which is unreliable and invites significant variation across institutions. Alternatively, they could adopt a "go slow" approach that includes multiple check-ins with the investigators as part of their oversight during the course of a specific research project.

Under current rules and policies regarding the welfare of nonhuman animals used in research, those who manage research with nonhuman animals are already looking at the nonhuman animals' overall health and well-being, including observing the nonhuman animal's behavior or conducting tests to identify signs of pain or stress. However, as discussed above they may not be considering whether the presence of human cells could lead to novel harms. In one view, this issue is not concerning, since the science is not there yet, leaving time for oversight to adapt and become more sensitive as the science evolves. Yet oversight committees may need assistance knowing *what* to look for, and there is not yet guidance about what types of changes in the behavior of a nonhuman animal should be cause for concern.[53] By bringing together appropriate expertise from the different committees, and possibly including an animal behaviorist as described above, institutions may better be able to address these overlapping concerns and make recommendations jointly to assure the research moves forward ethically. It is important for all involved with the research, investigators, lab staff, animal care staff, vet staff, and IACUCs to work together and to be vigilant about potential changes (for better or worse) in the nonhuman animals' well-being and health.

> **Recommendation #8:** *There should be a regularly convened national forum where representatives from U.S. research institutions can discuss ethics, governance, and oversight challenges pertaining to chimeric research (whether in the context of larger discussions about other areas of science or as a standalone topic) including issues related to the welfare of nonhuman animals containing human cells*.

A centralized forum for discussions among institutions, review board members, and scientists about chimeric research can help identify emerging ethical challenges and facilitate sharing of useful oversight approaches. One barrier to this kind of cross-institutional collaboration that may warrant further attention is institutional reluctance to share details about their research with potential competitors. Nevertheless, a forum for some kind of national discussion would help researchers, funders, and oversight officials to anticipate the ethical challenges associated with future research and share governance and oversight strategies.

These discussions could address approaches to oversight. For example, some institutions have adapted oversight approaches for stem cell research to anticipate and accommodate rapidly changing and cutting-edge science. Some ESCRO committees have expanded their scope to include oversight of research with hiPSCs and research that creates human gametes and studies involving making changes to human embryos, including mitochondrial replacement and other research "in the gap" that existing committees do not cover. There is currently no regular forum in which these oversight committees can share their experiences and learn from each other.

A national forum could also be a chance to anticipate governance needs. Even if concerns about the emergence of "human-like" behaviors or capacities in nonhuman animals that contain human stem cells are far ahead of the current state of the science, it is important for researchers and oversight officials to think ahead together. A centralized information-gathering and discussion forum could help IRBs, ESCRO committees, and IACUCs prepare for future research developments in an informed way that allows for consistent approaches across institutions and the development of a body of best practices.

The nonprofit membership organization Public Responsibility in Medicine & Research (PRIM&R) could be the venue for such a national forum. PRIM&R holds an annual conference that brings together research oversight professionals to address a wide range of ethical, regulatory, and operational issues in research with human beings and with nonhuman animals. PRIM&R members include professionals involved with oversight of research involving stem cells, animals, and human participants. Other possible hosts of an annual forum would be the NASEM or the NIH's Novel and Exceptional Technology and Research Advisory Committee (NExTRAC). The NASEM convenes experts to address current and future challenges related to science and technology, and those experts' findings and recommendations are highly respected and often influence research institutions' policies and practices (NASEM's guidelines for embryonic stem cell research were very influential in the development of ESCRO committees). The NExTRAC is a new federal advisory committee that provides recommendations to the NIH director about the scientific, safety, and ethical issues associated with emerging biotechnologies. Both the NASEM and the NExTRAC make some of their meetings open to the public, and PRIM&R conferences are open to the public, although there is a conference fee.

> **Recommendation #9:** *Scientists, funders, research institutions, research advocates, and journalists should provide to the public clear information about chimeric research and the various scientific reasons for conducting specific studies. They should avoid using technical scientific language and references (either in writing or with visuals) to mythological chimeras. Visuals that depict realistic in vitro and in vivo chimeric research would be more helpful in clearly communicating to the public the nature and purposes of the research*.

There is a special imperative for research funders, researchers, and research institutions to communicate well with the public about scientific research that is known to be troubling to some people. Because some kinds of chimeric research are known to be controversial or morally concerning, those involved in this work have a heightened responsibility to proactively anticipate concerns and to clearly communicate to the public and to journalists the state of the science and the current issues. However, public communication should not begin from the assumption that people with deeply held religious beliefs and moral values about the species boundaries, the moral status of human embryos, or the use of nonhuman animals in research are unable to understand the research that is proposed and conducted. Rather, transparency in a democratic society requires public communication about science in lay terms, first and foremost, regardless of whether some members of the public support or oppose the science under discussion. For example, while it is commendable that the NIH invited public comments on a proposed funding policy for chimeric research, the

notice and request for comments in the *Federal Register* were written in technical scientific language, which is not optimal for communicating complex and potentially contested science to the general public.[54] Our research team's preliminary analysis of a sample of the comments submitted to the NIH indicate that thousands of the comments used identical or nearly identical language expressing opposition to chimeric research and reflected a misunderstanding of the issues the NIH had raised.

Institutions where chimeric research is conducted may be reluctant to provide detailed information to the public about such research or to provide details about members of committees that oversee the research. Many people object to research with hESCs, to chimeric research, and to research with nonhuman animals. And researchers and institutions that conduct research with nonhuman animals have sometimes received threats for doing so. What matters, as a minimum baseline, is that research institutions are transparent about the governance and oversight mechanisms in place to ensure that chimeric research is conducted according to ethical standards, institutional and funder policies, and relevant laws and regulations. Researchers should continue to disclose in presentations and publications about their research—but also in interviews with journalists—which oversight committees reviewed and approved their studies. Many journals publishing this type of research now do an ethical review of the submitted manuscript which includes asking for a description of the oversight in the methods. All journals publishing the results of chimeric research should adopt the practice.

Since some members of the public may be opposed to various kinds of chimeric research, scientists and their institutions should acknowledge such opposition, explain why they are doing the work, why they see it as important, and acknowledge any ethical and other concerns that arise about the research. Funders of this chimeric research—particularly funders using public dollars—should do the same. In this way, research institutions and scientists and their funders are accountable for providing reasons for their funding and research, along with some details about it.[55] This approach to public communication was used when many scientists who supported and/or conducted research with hESCs and human fetal tissue/cell lines tried to be open and clear about the importance of using these human biological materials in certain types of research while acknowledging the ethical issues involved and the opposition to such research by some members of the public.[56] Clear and open communication with the public reflects the ethos of responsible science and research transparency in a democratic society.

It is also important that journalists communicate clearly to the public about chimeric research. This means not only emphasizing the potential benefits of the research for the development of preventive and treatment interventions for humans but also acknowledging the ethical concerns such research raises, including concerns about research with nonhuman animals. And just as importantly, journalists should avoid using misleading references to mythological stories about, and cartooned images of, nonhuman animals with human features.[57]

Recommendation #10: *In recognition of the importance of public communication about chimeric studies, funders should provide financial support to cover*

collaboration between researchers and communications staff. Research institutions should assert the value of effective lay communication for continued scientific progress by recognizing such efforts when granting tenure and supporting access to a robust communications staff. Academic journals can contribute to this endeavor by allowing or requiring that lay summaries, other documents, or video abstracts appear with a published scientific article. With more readily available lay language, journalists and their editors should endeavor to represent the science as clearly, simply, and accurately as possible.

Innovative public communication has historically been treated as beyond the scope of scientific research. It requires an investment of time and money, and scientists' efforts on this front are rarely afforded recognition or prestige. In the contemporary information landscape, however, science is increasingly exposed to public notice and attention. To meet growing interest in scientific activities, communication strategies should be developed that are lay friendly and acknowledge the ethical and governance approaches about the research in question.

Recent work in genomics may offer insight into effective public communication strategies. Research groups have used various approaches to clarify and explain work that is easily misinterpreted, may be controversial, or has a troubling history. In 2019, for example, a genome-wide association study of same-sex sexual behavior appeared in the journal *Science* on the same day that the research team released a collection of other articles, videos, and even an animation intended for journalists and the lay public.[58]

For the strategies described above, connecting the publication of a scientific article with the accompanying materials can be challenging. Someone who comes across the article via a direct internet link or scientific database may not see the communications materials that have been developed in tandem. To address this challenge, other innovative communication strategies could be used. For example, the journal *Autism Research* requires authors to provide a summary of the science "in more lay terms intended to make the research findings presented in the article accessible to those outside the scientific community, especially families" with individuals on the autism spectrum. Although the primary public audience for communicating information about chimeric research may not be a patient population, lay abstracts and video summaries can contribute to the broader project of engaging in effective public communication about complex scientific research and the ethical issues the research raises.[59] Communication tools such as videos and other materials that are developed can build off one another to facilitate easier production for other research teams that want to develop robust public communication materials.

While we advocate for improved and more frequent public communication regarding the methods and goals of chimeric studies, this report does not call for research funders, researchers, or research institutions to conduct public engagement activities regarding this area of science. Others have called for public engagement to inform this type of research[60] as well as other types of scientific research that raise ethical issues (e.g., hESC research, human genome editing research, and research involving gene drives to genetically modify nonhuman organisms).[61] Yet calls for public engagement tend to list a smorgasbord of

possible engagement activities without taking a firm position on whether decision-makers—i.e., funders, researchers, and research institutions—ought to follow the advice of public engagement participants. Indeed, public engagement activities often take place *after* the research in question is in progress or has been completed. There is value in learning—through various public engagement activities and social science research—about the publics' perceptions and concerns regarding chimeric research. We leave it to others to address who should conduct public engagement and how, and but note that the views of those who participate in engagement activities is unlikely to play a definitive role in deciding whether and how chimeric research is conducted or the oversight policies and practices affecting such research.

Acknowledgments

Research reported in this publication was fully supported by the National Human Genome Research Institute of the National Institutes of Health under award number R01HG010168. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

The authors wish to thank Isabel Bolo for her work as project manager-research assistant to this project and Ben Curran Wills for his work reviewing and analyzing the public comments submitted to the NIH and developing manuscripts on this topic.

The Hastings-CWRU Research Team

The Hastings Center

Josephine Johnston

Karen Maschke

Carolyn Neuhaus

Margaret M. Matthews

Isabel Bolo

Case Western Reserve University

Insoo Hyun (now at Museum of Science, Boston)

Patricia Marshall

Kaitlynn P. Craig

Project Work Group

Kara Drolet – Oregon Health & Science University

Henry T. Greely – Stanford University

Lori R. Hill – MD Anderson Cancer Center

Amy Hinterberger – King's College London

Elisa A. Hurley – PRIM&R

Robert Kesterson – University of Alabama at Birmingham

Jonathan Kimmelman – McGill University

Nancy M. P. King – Wake Forest University School of Medicine

Geoffrey Lomax – California Institute for Regenerative Medicine

Melissa J. Lopes – ESCRO Committee

P. Pearl O'Rourke – Harvard Medical School

Brendan Parent – NYU Grossman School of Medicine

Steven Peckman – University of California, Los Angeles

Monika Piotrowska – SUNY at Albany

May Schwarz – The Salk Institute for Biological Studies

Jeff Sebo – New York University

Robert Streiffer – University of Wisconsin-Madison

Chris Stodgell – University of Rochester

Lorenz Studer – Memorial Sloan Kettering Cancer Center

Amy Wilkerson – The Rockefeller University

CITATIONS

1. DeWitt N, "Biologists Divided Over Proposal to Create Human-Mouse Embryos," Nature 420, no. 6913 (2002): 255–56; [PubMed: 12447402] Behringer R, "Human-Animal Chimeras in Biomedical Research," Cell Stem Cell 1 (2007): 259–262. [PubMed: 18371360]
2. Ramzy A et al. , "Implanted Pluripotent Stem-Cell-Derived Pancreatic Endoderm Cells Secrete Glucose-Responsive C-Peptide in Patients with Type 1 Diabetes," Cell Stem Cell 28, no. 12 (2021): 2047–2061.e5. [PubMed: 34861146]
3. Wu J et al. , " Interspecies Chimerism with Mammalian Pluripotent Stem Cells," Cell 168, no. 3 (2017): 473–486; [PubMed: 28129541] Wu J, et al. , " Stem Cells and Interspecies Chimaeras," Nature 540, no. 7631 (2016): 51–59; [PubMed: 27905428] Wu J et al. , " Generation of Human Organs in Pigs via Interspecies Blastocyst Complementation," Reproduction in Domestic Animals 51 (2016): 18–24;Kobayashi T, Kato-Itoh M, and Nakauchi H, " Targeted Organ Generation Using MIXL1-Inducible Mouse Pluripotent Stem Cells in Blastocyst Complementation," Stem Cells and Development 24, no. 2 (2015): 182–189; [PubMed: 25192056] Rashid T, Kobayashi T, and Hiromitsu N, "Revisiting the Flight of Icarus: Making Human Organs from PSCs with Large Animal Chimeras," Cell Stem Cell 15, no. 4 (2014): 406–409. [PubMed: 25280216]
4. Wu J, et al. , " Stem Cells and Interspecies Chimaeras," Nature 540, no. 7631 (2016): 51–59; [PubMed: 27905428] Hyun I et al. , "Ethical Standards for Human-to-Animal Chimera Experiments for Stem Cell Research," Cell Stem Cell 1, no. 2 (2007): 159–163. [PubMed: 18383627]

5. Streiffer R, “At the Edge of Humanity: Human Stem Cells, Chimeras, and Moral Status,” Kennedy Institute of Ethics Journal 15, no. 4 (2005): 347–370. [PubMed: 16453949]

6. Robert JS and Baylis F, “Crossing Species Boundaries,” American Journal of Bioethics 3, no. 3 (2003): 1–13.

7. Magnani TA, “ The Patentability of Human-Animal Chimeras,” Berkeley Technology Law Journal 14 (1999): 443–460. [PubMed: 15732205]

8. Kopinski NE, “ Human-Nonhuman Chimeras: A Regulatory Proposal on the Blurring of Species Lines,” Boston College Law Review 45, no. 3 (2003): 619–666.

9. Institute of Medicine and National Research Council, Guidelines for Human Embryonic Stem Cell Research (Washington, D.C.: The National Academies Press, 2005).

10. Institute of Medicine and National Research Council, Final Report of the National Academies’ Human Embryonic Stem Cell Research Advisory Committee and 2010 Amendments to the National Academies’ Guidelines for Human Embryonic Stem Cell Research (Washington, D.C.: The National Academies Press, 2010).

11. ISSCR International Human Embryonic Stem Cell Research Task Force, “Guidelines for Embryonic Stem Cell Research,” Current Protocols in Stem Cell Biology Appendix 1 (June 2007): Appendix 1A.

12. International Society for Stem Cell Research, ”Guidelines for Stem Cell Research and Clinical Translation,” (2021), https://www.isscr.org/policy/guidelines-for-stem-cell-research-and-clinical-translation;Hyun I et al. , “ISSCR Guidelines for the Transfer of Human Pluripotent Stem Cells and Their Direct Derivatives into Animal Hosts,” Stem Cell Reports 16, no. 6 (2021): 1409–1415. [PubMed: 34048695]

13. National Academies of Sciences, Engineering, and Medicine, The Emerging Field of Human Neural Organoids, Transplants, and Chimeras: Science, Ethics, and Governance (Washington, D.C.: National Academies Press, 2021).

14. National Institutes of Health, NIH Research Involving Introduction of Human Pluripotent Cells into Non-Human Vertebrate Animal Pre-Gastrulation Embryos (NIH, August 4, 2016), https://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-158.html.

15. Craig K, “When Dogs Play Cards: Interviews with Scientists, Researchers, and Oversight Committee Members on Ethical Guidelines for Human-Animal Chimera Research” (presentation, ELSIConversations, March 19, 2021), https://elsihub.org/video/which-public-what-comments-analysis-public-comments-human-animal-chimera-research-submitted;Craig K, “When Dogs Play Cards: Interviews with Scientists, Researchers, and Oversight Committee Members on Ethical Guidelines for Human-Animal Chimera Research” (presentation, American Society for Bioethics and Humanities, October 2020).

16. Stem cells are cells that can self-renew and create other, new cells. Pluripotent stem cells can create all the cells and tissues in the human body. Cells derived directly from stem cells--stem cell derivatives--are descendants of stem cells, which can further differentiate to create specialized cell types, as well as more distal, differentiated cells. For more information see the National Institutes of Health, ”Stem Cell Basics,” https://stemcells.nih.gov/info/basics/stc-basics.

17. Scharping N, “Why Scientists Have Been Creating Chimeras in the Lab for Decades,” Discover, May 19, 2021, https://www.discovermagazine.com/health/why-scientists-have-been-creating-chimeras-in-the-lab-for-decades;Savulescu J and Palacios-González C, “First Human-Monkey Embryos Created – A Small Step Towards a Huge Ethical Problem,” The Conversation, April 22, 2021, https://theconversation.com/first-human-monkey-embryos-created-a-small-step-towards-a-huge-ethical-problem-159355;Gallagher J, “Human-Pig ‘Chimera Embryos’ Detailed,” BBC News, January 26, 2017, https://www.bbc.com/news/health-38717930.

18. National Academies of Sciences, Engineering, and Medicine, The Emerging Field of Human Neural Organoids, Transplants, and Chimeras: Science, Ethics, and Governance (Washington, D.C.: National Academies Press, 2021).

19. Academy of Medical Sciences, Animals Containing Human Materials (United Kingdom: Academy of Medical Sciences, 2011), https://acmedsci.ac.uk/policy/policy-projects/animals-containing-human-material.

20. Kwisda K, White L, and Hübner D, “ Ethical Arguments Concerning Human-Animal Chimera Research: A Systematic Review,” BMC Medical Ethics 21, no. 1 (2020): 1–14; [PubMed:

31906925] for an important exception see Crozier GK et al., “12 Nonhuman, All Too Human: Toward Developing Policies for Ethical Chimera Research,” in Neuroethics and Nonhuman Animals, ed. Johnson LSM, Fenton A, and Shriver A (Springer Nature, 2020), 205–219.

21. Greely HT et al. , “Thinking About the Human Neuron Mouse,” The American Journal of Bioethics 7, no. 5 (2007): 27–40.
22. DeGrazia D, Taking Animals Seriously: Mental Life and Moral Status (Cambridge University Press, 1996).
23. Frey RG, “Utilitarianism and Animals,” in The Oxford Handbook of Animal Ethics, ed. Beauchamp TL and Frey RG (New York: Oxford University Press, 2011), 184.
24. Russell WMS and Burch RL, The Principles of Humane Experimental Technique (London: Methuen, 1959).
25. International Society for Stem Cell Research, ”Guidelines for Stem Cell Research and Clinical Translation,” (2021), https://www.isscr.org/policy/guidelines-for-stem-cell-research-and-clinical-translation;Hyun I et al. , “ISSCR Guidelines for the Transfer of Human Pluripotent Stem Cells and Their Direct Derivatives into Animal Hosts,” Stem Cell Reports 16, no. 6 (2021): 1409–1415. [PubMed: 34048695]
26. Kwisda K, White L, and Hübner D, “ Ethical Arguments Concerning Human-Animal Chimera Research: A Systematic Review,” BMC Medical Ethics 21, no. 1 (2020): 1–14. [PubMed: 31906925]
27. Hartung T, “Look Back in Anger – What Clinical Studies Tell Us about Preclinical Work,” ALTEX 30, no. 3 (2013): 275–91; [PubMed: 23861075] McGonigle P, and Ruggeri B, “Animal Models of Human Disease: Challenges in Enabling Translation,” Biochemical Pharmacology 87, no. 1 (2014): 162–71; [PubMed: 23954708] Sena ES et al. , “Publication Bias in Reports of Animal Stroke Studies Leads to Major Overstatement of Efficacy,” ed. Roberts I, PLoS Biology 8, no. 3 (2010): e1000344; [PubMed: 20361022] Macleod M and Mohan S, “Reproducibility and Rigor in Animal-Based Research,” ILAR Journal 60, no. 1 (December 31, 2019): 17–23; [PubMed: 31687758] Kilkenny C et al. , “Survey of the Quality of Experimental Design, Statistical Analysis and Reporting of Research Using Animals,” PLoS ONE 4, no. 11 (November 30, 2009): e7824. [PubMed: 19956596]
28. Kimmelman J, Gene Transfer and the Ethics of First-in-Human Research: Lost in Translation (Cambridge: Cambridge University Press, 2010);Kimmelman J and London AJ, “The Structure of Clinical Translation: *Efficiency, Information, and Ethics*,” Hastings Center Report 45, no. 2 (March 2015): 27–39. [PubMed: 25628068]
29. Davies GF, “Harm-Benefit Analysis: Opportunities for Enhancing Ethical Review in Animal Research,” Lab Animal 47, no. 3 (March 2018): 57–58; [PubMed: 29483693] Tannenbaum J, “The Pursuit and Advancement of Knowledge as a Justification for the Use of Animals in Research,” ILAR Journal 60, no. 3 (December 31, 2019): 347–65.
30. Liu Z et al. , “ Autism-like Behaviours and Germline Transmission in Transgenic Monkeys Overexpressing MeCP2,” Nature 530, no. 7588 (2016): 98–102; [PubMed: 26808898] Garner JP, “The Mouse in the Room: The Distinction Between Regulations and Ethics,” in Principles of Animal Research Ethics, ed. Beauchamps TL and Degrazia D (Oxford University Press, 2020), 82.
31. Millman ST et al. , “The Impact of Applied Ethologists and the International Society for Applied Ethology in Improving Animal Welfare,” Applied Animal Behaviour Science 86, no. 3–4 (June 2004): 299–311.
32. Collins FS, “NIH Will No Longer Support Biomedical Research on Chimpanzees,” National Institutes of Health, November 17, 2015, https://www.nih.gov/about-nih/who-we-are/nih-director/statements/nih-will-no-longer-support-biomedical-research-chimpanzees.
33. Andrews K et al., Chimpanzee Rights: The Philosophers’ Brief (Routledge, 2018);Nonhuman Rights Project, Inc. ex rel. Tommy v. Lavery, 54 N.Y.S.3d 392, 394 (2017).
34. Subbaraman N, “The US Is Boosting Funding for Research Monkeys in the Wake of COVID,” Nature 595, no. 7869 (2021): 633–634. [PubMed: 34267388]
35. Ferdowsian H et al. , “A Belmont Report for Animals?,” Cambridge Quarterly of Healthcare Ethics 29, no. 1 (2020): 19–37; [PubMed: 31581963] Sebo J, “Kantianism for Humans, Utilitarianism for Nonhumans? Yes and No,” Philosophical Studies (2022): 1–20.

36. Craig K, “When Dogs Play Cards: Interviews with Scientists, Researchers, and Oversight Committee Members on Ethical Guidelines for Human-Animal Chimera Research” (presentation, ELSIConversations, March 19, 2021), https://elsihub.org/video/which-public-what-comments-analysis-public-comments-human-animal-chimera-research-submitted;Craig K, “When Dogs Play Cards: Interviews with Scientists, Researchers, and Oversight Committee Members on Ethical Guidelines for Human-Animal Chimera Research” (presentation, American Society for Bioethics and Humanities, October 2020).
37. Funk C and Hefferon M, “Most Americans Accept Genetic Engineering of Animals that Benefits Human Health, but Many Oppose Other Uses,” Pew Research Center, August 16, 2018, https://www.pewresearch.org/science/2018/08/16/most-americans-accept-genetic-engineering-of-animals-that-benefits-human-health-but-many-oppose-other-uses/;Crane A et al. , “ The American Public Is Ready to Accept Human-Animal Chimera Research,” Stem Cell Reports 15, no. 4 (2020): 804–10; [PubMed: 33007202] Wills BC, “Which Public, What Comments? An Analysis of Public Comments on Human-Animal Chimera Research Submitted to the National Institutes of Health” (presentation, ELSIConversations, March 19, 2021), https://elsihub.org/video/which-public-what-comments-analysis-public-comments-human-animal-chimera-research-submitted.
38. Thomson JA et al. , “ Embryonic Stem Cell Lines Derived from Human Blastocysts,” Science 282, no. 5391 (1998): 1145–1147. [PubMed: 9804556]
39. President’s Council on Bioethics, Monitoring Stem Cell Research (Washington D.C.: 2004), http://bioethics.georgetown.edu/pcbe/reports/stemcell/.
40. Gallup, “Stem Cell Research,” Gallup News, 2022, https://news.gallup.com/poll/21676/stem-cell-research.aspx;Wills BC, “Which Public, What Comments? An Analysis of Public Comments on Human-Animal Chimera Research Submitted to the National Institutes of Health” (presentation, ELSIConversations, March 19, 2021), https://elsihub.org/video/which-public-what-comments-analysis-public-comments-human-animal-chimera-research-submitted.
41. Karpowicz P, Cohen CB, and Van der Kooy D, “Developing Human-Nonhuman Chimeras in Human Stem Cell Research: Ethical Issues and Boundaries,” Kennedy Institute of Ethics Journal 15, no. 2 (2005): 107–134; [PubMed: 16149204] Johnston J and Eliot C, “Chimeras and ‘Human Dignity,’” The American Journal of Bioethics 3, no. 3 (2003): 6–8;de Melo-Martín I, “Chimeras and Human Dignity,” Kennedy Institute of Ethics Journal 18, no. 4 (2008): 331–346. [PubMed: 19143408]
42. International Society for Stem Cell Research, “Guidelines for Stem Cell Research and Clinical Translation,” (2021), https://www.isscr.org/policy/guidelines-for-stem-cell-research-and-clinical-translation;Hyun I et al. , “ISSCR Guidelines for the Transfer of Human Pluripotent Stem Cells and Their Direct Derivatives into Animal Hosts,” Stem Cell Reports 16, no. 6 (2021): 1409–1415. [PubMed: 34048695]
43. Robert JS and Baylis F, “Crossing Species Boundaries,” American Journal of Bioethics 3, no. 3 (2003): 1–13.
44. Corbey R and Lanjouw A, The Politics of Species: Reshaping Our Relationships with Other Animals, (Cambridge: Cambridge University Press, 2013).
45. Ereshefsky M, “Species,” in The Stanford Encyclopedia of Philosophy, ed. Zalta EN (Stanford University: Metaphysics Research Lab, 2022), http://plato.stanford.edu/entries/species/.
46. Swiss Institute of Bioinformatics, “Humans and chimpanzees share 99% of the same DNA. This is the 1% difference,” Genetic Literacy Project, January 18, 2021, https://geneticliteracyproject.org/2021/01/18/humans-and-chimpanzees-share-99-of-the-same-dna-this-is-the-1-difference/#).
47. Singer P, Animal Liberation: A New Ethics for Our Treatment of Animals (New York: The New York Review of Book, 1990).
48. Lo B et al. , “ Informed Consent in Human Oocyte, Embryo, and Embryonic Stem Cell Research,” Fertility and Sterility 82, no. 3 (2004): 559–563. [PubMed: 15374695]
49. National Academies of Sciences, Engineering, and Medicine, The Emerging Field of Human Neural Organoids, Transplants, and Chimeras: Science, Ethics, and Governance (Washington, D.C.: National Academies Press, 2021).
50. 42 C.F.R. §50 (F)

51. Hyun I, Wilkerson A, and Johnston J, “Embryology Policy: Revisit the 14-Day Rule,” Nature 533, no. 7602 (2016): 169–171. [PubMed: 27172031]
52. Consolidated Appropriations Act, H.R. 2471, 117th Cong. (2022), https://www.congress.gov/bill/117th-congress/house-bill/2471/text.
53. Piotrowska M, “Transferring Morality to Human–Nonhuman Chimeras,” The American Journal of Bioethics 14, no. 2 (2014): 4–12;Piotrowska M, “Rethinking the Oversight Conditions of Human–Animal Chimera Research,” Bioethics 35, no. 1 (2021): 98–104. [PubMed: 32783224]
54. National Institutes of Health, “Request for Public Comment on the Proposed Changes to the NIH Guidelines for Human Stem Cell Research and the Proposed Scope of an NIH Steering Committee’s Consideration of Certain Human-Animal Chimera Research,” Federal Register 81, No. 151 (Office of the Federal Register, National Archives and Records Administration, Friday, August 5, 2016), 51921–51923, https://www.federalregister.gov/documents/2016/08/05/2016-18601/request-for-public-comment-on-the-proposed-changes-to-the-nih-guidelines-for-human-stem-cell.
55. Carbone L, “Open Transparent Communication about Animals in Laboratories: Dialog for Multiple Voices and Multiple Audiences,” Animals 11, no. 2 (2021): 368. [PubMed: 33540590]
56. Castelvecchi D, “How Human Embryonic Stem Cells Sparked a Revolution,” Nature 555, no. 7697 (2018): 428–30. [PubMed: 29565377]
57. Hagan-Brown A, Favaretto M, Borry P, “Newspaper Coverage of Human-Pig Chimera Research: A Qualitative Study on Select Media Coverage of Scientific Breakthrough,” Xenotransplantation 24, no. 4 (2017): e12317.
58. Ganna A, et al. , “Large-scale GWAS Reveals Insights into the Genetic Architecture of Same-Sex Sexual Behavior,” Science 365, no. 6456 (2019): eaat7693; [PubMed: 31467194] Broad Communications, “Perspectives on the Complex Genetics of Same-Sex Sexual Behavior,” Broad Institute, August 29, 2019, https://www.broadinstitute.org/news/perspectives-complex-genetics-same-sex-sexual-behavior.
59. Kuehne LM and Olden JD. “Opinion: Lay Summaries Needed to Enhance Science Communication,” Proceedings of the National Academy of Sciences 112, no. 12 (2015): 3585–3586;Schmaltz A, “On the Utility of Lay Summaries and AI Safety Disclosures: Toward Robust, Open Research Oversight,” in Proceedings of the Second ACL Workshop on Ethics in Natural Language Processing, ed. Alfano M et al. (New Orleans: Association for Computational Linguistics, 2018), 1–6.
60. Inoue Y, Shineha R, and Yashiro Y, “Current Public Support for Human-Animal Chimera Research in Japan Is Limited, Despite High Levels of Scientific Approval,” Cell Stem Cell 19, no. 2 (2016): 152–53; [PubMed: 27494672] National Academies of Sciences, Engineering, and Medicine, The Emerging Field of Human Neural Organoids, Transplants, and Chimeras: Science, Ethics, and Governance (Washington, D.C.: National Academies Press, 2021), 103;National Institutes of Health, “Request for Public Comment on the Proposed Changes to the NIH Guidelines for Human Stem Cell Research and the Proposed Scope of an NIH Steering Committee’s Consideration of Certain Human-Animal Chimera Research,” Federal Register 81, No. 151 (Office of the Federal Register, National Archives and Records Administration, Friday, August 5, 2016), 51921–51923, https://www.federalregister.gov/documents/2016/08/05/2016-18601/request-for-public-comment-on-the-proposed-changes-to-the-nih-guidelines-for-human-stem-cell.
61. Mohr A and Raman S, “Representing the Public in Public Engagement: The Case of the 2008 UK Stem Cell Dialogue,” ed. Marris C and Rose N, PLoS Biology 10, no. 11 (2012): e1001418; [PubMed: 23152719] Andorno R et al. , “Geneva Statement on Heritable Human Genome Editing: The Need for Course Correction,” Trends in Biotechnology 38, no. 4 (2020): 351–54; [PubMed: 32014274] National Academies of Sciences, Engineering, and Medicine, Gene Drives on the Horizon: Advancing Science, Navigating Uncertainty, and Aligning Research with Public Values (Washington, D.C.: The National Academies Press, 2016). The NASEM Brain Organoid report disusses and cites the other NASEM reports that call for public engagement: https://nap.nationalacademies.org/read/26078/chapter/7#92
62. Halme D and Kessler D, “FDA Regulation of Stem-Cell-Based Therapies,” New England Journal of Medicine 355, no. 16 (2006): 1730–1735. [PubMed: 17050899]

63. De Los Angeles A, “Monkey Embryos Cultured to 20 Days,” Stem Cells and Development 29, no. 13 (2020): 807–810; [PubMed: 32375565] De Los Angeles A et al. , “ Human-Monkey Chimeras for Modeling Human Disease: Opportunities and Challenges,” Chimera Research (2019): 221–231.
64. Tan T et al. , “Chimeric Contribution of Human Extended Pluripotent Stem Cells to Monkey Embryos Ex Vivo,” Cell 184, no. 8 (2021): 2020–2032. [PubMed: 33861963]
65. Coghlan A, “The Smart Mouse with the Half-Human Brain,” New Scientist, December 1, 2014. newscientist.com/article/dn26639-the-smart-mouse-with-the-half-human-brain/.
66. Han X et al. , “ Forebrain Engraftment by Human Glial Progenitor Cells Enhances Synaptic Plasticity and Learning in Adult Mice,” Cell Stem Cell 12, no. 3 (2013): 342–353. [PubMed: 23472873]
67. Crane A et al. , “Concise Review: Human-Animal Neurological Chimeras: Humanized Animals or Human Cells in an Animal?,” Stem Cells 37, no. 4 (2019): 444–452. [PubMed: 30629789]
68. United States, “Health Research Extension Act of 1985. Public Law 99–158,” United States Statutes at Large 99, Title IV (1985): Sections 1–12.
69. National Research Council, Guide for the Care and Use of Laboratory Animals: Eighth Edition (Washington, D.C.: National Academies Press, 2011), 28.
70. Craig K, “When Dogs Play Cards: Interviews with Scientists, Researchers, and Oversight Committee Members on Ethical Guidelines for Human-Animal Chimera Research” (presentation, ELSIConversations, March 19, 2021), https://elsihub.org/video/which-public-what-comments-analysis-public-comments-human-animal-chimera-research-submitted;Craig K, “When Dogs Play Cards: Interviews with Scientists, Researchers, and Oversight Committee Members on Ethical Guidelines for Human-Animal Chimera Research” (presentation, American Society for Bioethics and Humanities, October 2020).
71. 45 C.F.R. §46
72. 45 C.F.R. §46.111
73. 21 C.F.R. §56
74. Macintosh KL, “Chimeras, Hybrids, and Cybrids: How Essentialism Distorts the Law and Stymies Scientific Research,” Arizona State Law Journal 47 (2015):183–233;Human-Animal Chimera Prohibition Act of 2021, H.R. 1800, 117th Cong (2021), https://www.congress.gov/117/bills/s1800/BILLS-117s1800is.pdf.
75. AZ Rev Stat § 36–2312 (2016); LA Rev Stat § 14:89.6.
76. AZ Rev Stat § 36–2312 (2016); LA Rev Stat § 14:89.6.
77. National Institutes of Health, NIH Research Involving Introduction of Human Pluripotent Cells into Non-Human Vertebrate Animal Pre-Gastrulation Embryos (NIH, September 23, 2015), https://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-158.html.
78. Wolinetz CD, “Next Steps on Research Using Animal Embryos Containing Human Cells,” National Institutes of Health Office of Science Policy, August 4, 2016, https://osp.od.nih.gov/2016/08/04/next-steps-on-research-using-animal-embryos-containing-human-cells/;National Institutes of Health, “Request for Public Comment on the Proposed Changes to the NIH Guidelines for Human Stem Cell Research and the Proposed Scope of an NIH Steering Committee’s Consideration of Certain Human-Animal Chimera Research,” Federal Register 81, No. 151 (Office of the Federal Register, National Archives and Records Administration, Friday, August 5, 2016), 51921–51923, https://www.federalregister.gov/documents/2016/08/05/2016-18601/request-for-public-comment-on-the-proposed-changes-to-the-nih-guidelines-for-human-stem-cell.
79. Bolo I, Wills BC and Maschke KJ, “Public Attitudes toward Human-Animal Chimera Research May Be More Complicated than They Appear,” Stem Cell Reports 16, no.2 (2021): 225–6. [PubMed: 33567291]
80. California Institute of Regenerative Medicine, “The CIRM Medical and Ethical Standards Regulations,” (California: May 2012), https://www.cirm.ca.gov/sites/default/files/files/board_meetings/CIRM_MES_regulations_Full_Revised_07_17_2013.pdf.
81. Dietz AG, Goldman SA, and Nedergaard M, “ Glial Cells in Schizophrenia: A Unified Hypothesis,” The Lancet Psychiatry 7, no. 3 (2020): 272–81. [PubMed: 31704113]

82. Institute of Medicine and National Research Council, Final Report of the National Academies' Human Embryonic Stem Cell Research Advisory Committee and 2010 Amendments to the National Academies' Guidelines for Human Embryonic Stem Cell Research (Washington, D.C.: The National Academies Press, 2010);International Society for Stem Cell Research, Guidelines for the Field of Stem Cell Research and Regenerative Medicine (2021), https://www.isscr.org/policy/guidelines-for-stem-cell-research-and-clinical-translation.

83. Institute of Medicine and National Research Council, Final Report of the National Academies' Human Embryonic Stem Cell Research Advisory Committee and 2010 Amendments to the National Academies' Guidelines for Human Embryonic Stem Cell Research (Washington, D.C.: The National Academies Press, 2010); 32–33.

84. International Society for Stem Cell Research, "Guidelines for Stem Cell Research and Clinical Translation," (2021), https://www.isscr.org/policy/guidelines-for-stem-cell-research-and-clinical-translation;Hyun I et al. , "ISSCR Guidelines for the Transfer of Human Pluripotent Stem Cells and Their Direct Derivatives into Animal Hosts," Stem Cell Reports 16, no. 6 (2021): 1409–1415. [PubMed: 34048695]

85. Institute of Medicine and National Research Council, Final Report of the National Academies' Human Embryonic Stem Cell Research Advisory Committee and 2010 Amendments to the National Academies' Guidelines for Human Embryonic Stem Cell Research (Washington, D.C.: The National Academies Press, 2010); 35.

BOX 1:

Chimeric Research Today

Chimeric research involves the creation or use of embryos or animals carrying cell populations derived from two or more genetically distinct sources. Today, such research typically involves adding human cells derived from human embryos or other human stem cells to nonhuman embryos or nonhuman animals. Interest in the potential for cell-based therapeutic products for humans, including stem cell, gene addition, and gene editing interventions, has been an important driver of chimeric research. International regulatory frameworks typically require the developers of such interventions to demonstrate, in studies with nonhuman animals, that cell and gene addition products take root in the host and demonstrate an effect. In the larger regulatory context, these studies are intended to satisfy the safety and efficacy standard for moving from preclinical studies with nonhuman animals to human clinical trials.[62]

Although basic and translational chimeric research is progressing quickly, there are scientific challenges. In particular, thus far, the concentration of human cells in nonhuman animals and embryos has been low, especially when human stem cells are transplanted into a post-natal nonhuman animal. This may be due to the few weeks that chimeric embryos and fetuses are allowed to develop, or it may be due to differences in developmental timing between human and nonhuman cells. If human stem cells are introduced into a nonhuman animal fetus in utero or into a nonhuman animal embryo (especially if that embryo is then gestated), the percentage of human cells and their degree of physiological integration in the developing chimeric animal are predicted to be somewhat higher.

The degree of cellular integration may also be influenced by the evolutionary distance between species, with integration of human cells expected to be more substantial in closely related species, such as nonhuman primates. To investigate this possibility, researchers are studying the development in vitro of nonhuman primate embryos into which human stem cells have been transferred.[63] One team recently reported the survival of hPSCs in nonhuman primate embryos for 19 days in vitro at 7% maximum contribution of human cells, which while modest is higher than in prior studies with mouse and pig embryos.[64] Researchers have also proposed in vivo studies of nonhuman primates with human brain cells as a way to better understand psychiatric and neurological disorders, which have thus far proved difficult to accurately model in other nonhuman animals.

One concern raised about inserting human cells into nonhuman animals, including nonhuman primates, is that by biologically altering nonhuman animals early in development, scientists may end up changing them in morally relevant ways, especially if the nonhuman animals exhibit “humanlike” behaviors or capacities that they previously lacked.[65] A 2013 study raised this concern for some commentators when it was reported that mice with human glial cells in their forebrains showed learning speeds about two times greater than mice in the control group.[66] Specifically, the speed at which these chimeric mice were able to navigate mazes was enhanced, perhaps due to greater

efficiency of the human-derived supportive cells. The study reported no other changes to behavior or capabilities and has not been replicated. A recent review of neurological experiments with nonhuman animals suggests that significant neurological changes have yet to occur following transfer to human cells to nonhuman animals.[67] None of the 150 peer-reviewed scientific publications involving the transfer of human stem cells or their direct derivatives into the central nervous systems of mice, rats, or nonhuman primates reported cognitive or behavioral abilities that surpassed those exhibited by the animals' wild-type counterparts.

INTERSECTING GOVERNANCE OF CHIMERIC STUDIES

With a focus on the U.S., we summarize here the three governance frameworks shaping chimeric research.

BOX 2:

Research with nonhuman animals.

The Animal Welfare Act and its regulations set minimum standards for the care and treatment of nonhuman animals in research, exhibition, and transport and by dealers. The law applies to warm-blooded nonhuman animals, but not to many of the nonhuman animals most commonly used in laboratory research (specifically rats of the genus *Rattus* and mice of the genus *Mus* bred for use in research, estimated to account for over 95% of all research animals). One of the law's main functions is to require adequate housing, sanitation, nutrition, water, and veterinary care, including pain control, for research with covered nonhuman animals and to ensure that alternatives to using covered species are pursued when they are available. Where research is funded by the U.S. government, that research must also follow the U.S. Public Health Service (PHS) Policy on Humane Care and Use of Laboratory Animals and, through that policy, the *Guide for the Care and Use of Laboratory Animals (Guide)*, both of which cover a much larger range of nonhuman animals, applying to "any live, vertebrate animal used or intended for use in research, research training, experimentation, or biological testing or for related purposes."[68]

Under this framework, oversight committees typically called "institutional animal care and use committees" (IACUCs) review a broad range of chimeric research protocols. They review studies in which human cells will be inserted into post-natal nonhuman animals as well as those in which nonhuman embryos containing human cells will be gestated in nonhuman animals, even if only for a short time. IACUCs also review protocols that involve collecting gametes or embryos from nonhuman animals. IACUCs do not review purely in vitro studies using previously obtained nonhuman animal gametes or embryos.

When reviewing chimeric studies, IACUCs are not explicitly directed to consider issues specific to chimeric research. Neither the Animal Welfare Act and its regulations, the PHS Policy, the Guide, nor any other federal law or regulation directly addresses the possibility of research combining human cells with nonhuman animal cells in vitro or in post-natal nonhuman animals. IACUCs are, however, responsible for ongoing assessment of unexpected adverse outcomes, which could include unknown or unexpected phenotypes that may occur in genetically modified or other kinds of novel nonhuman animals. The Guide, for instance, notes that "more frequent monitoring of animals may be required" when novel changes are introduced into laboratory animals.[69] Despite this requirement, authors of this report with IACUC experience, as well as some respondents in this project's interview study[70] have not observed any differences in the review of studies involving chimeric research in terms of the welfare of the nonhuman animals at least thus far.

BOX 3:

Research with human subjects.

The “Federal Policy for the Protection of Human Subjects,” (the Common Rule) requires that research institutions use a specialized oversight committee called an institutional review board (IRB) to review and approve such research.[71] The IRB must ensure that risks to research subjects are minimized and reasonable, and that selection of subjects results in a just distribution of risks and benefits. With some exceptions, research subjects must give voluntary informed consent to participate in every study.[72] The U.S. Food and Drug Administration has similar rules for research to test the safety and efficacy of drugs, devices, and biologics.[73]

Under the Common Rule’s governance framework, no issues specific to chimeric research are mentioned. Nevertheless, IRBs will prospectively review proposed chimeric research studies if, but typically only if, the proposed study involves the collection of cells, gametes, or embryos from identifiable human donors. The IRB’s primary focus will be to ensure that researchers obtain voluntary informed consent from donors. If the proposed study will use cells, gametes or embryos that have been previously collected and stored for research use, and if identifying information about the human donors will not be passed onto researchers, then the study may not constitute “human subjects research” as defined in the regulations and may not require IRB review.

BOX 4:

Research with human embryos and human embryonic stem cells.

The governance frameworks most likely to directly reference chimeric research are various laws, rules, and guidelines developed since the late 1990s in response to the derivation of pluripotent stem cells from human embryos. These laws, regulations, policies, and guidelines differ, sometimes in contradictory ways.

There is no U.S. federal law addressing chimeric research. However, in the early 2000s and again in 2021, federal legislation was proposed that would have prohibited researchers in the U.S. from creating certain types of chimeric embryos and conducing certain types of research with human cells and nonhuman post-natal animals.[74] Closely-related law was passed at the state level in Arizona and Louisiana. In those states, prohibited experiments include creating "a human embryo into which a non-human cell or cells (or the component parts thereof) have been introduced."[75] Creation of "a non-human life form engineered such that it contains a human brain or a brain derived wholly or predominantly from human neural tissues" is also prohibited, as are chimeric studies resulting in a nonhuman animal that can produce human gametes.[76]

The U.S. does, however, place restrictions on the use of federal funds for chimeric research. Prior to 2015, the NIH provided some funding for chimeric research, although not if it involved the introduction of human pluripotent cells into nonhuman primate blastocysts. That year, the agency issued a moratorium on funding of research where hPSCs are inserted into all pre-gastrulation nonhuman animal embryos[77] while it gathered input on a proposal to create an internal steering committee to provide programmatic input to NIH Institute and Center Directors about funding decisions for two areas of research: studies involving the introduction of "human pluripotent cells into non-human vertebrate embryos, up through the end of gastrulation stage, with the exception of non-human primates, which would only be considered after the blastocyst stage," or studies involving the introduction of human cells into post-gastrulation non-human mammals (excluding rodents), where there could be either a substantial contribution or a substantial functional modification to the animal brain by the human cells."[78]

The NIH received more than 20,000 public comments on its proposed funding policy. Common themes in the comments included that chimeric research (1) violates religious commitments or beliefs about the use of human embryos and hESCs, (2) violates the moral status of human embryos, and (3) degrades the moral standing of humans vis-a-vis their relationship to nonhuman animals and to themselves as humans.[79] Many of the letters used verbatim or near-verbatim language, contending that chimeric research inappropriately and unnecessarily harms nonhuman animals, violates species boundaries, and involves inappropriate use of public money. In addition, some comment writers thought that the proposed policy was the wrong way to address the concerns that people have about this type of research. To date, the NIH has not acted on the funding proposal, and the 2015 moratorium remains in effect.

In response to federal funding restrictions for embryonic stem cell research, some U.S. states, in particular California and New York, developed their own funding streams with their own rules about chimeric research. California, for example, prohibits use of its funds for research in which hPSCs are introduced into nonhuman primate embryos, where nonhuman stem cells are introduced into human embryos, or where nonhuman chimeric animals breed.[80] Some institutions that have derived and now distribute hPSCs also restrict use of those cells. Restrictions mentioned or implied in donor's consent forms may prevent those stem cell lines being used in chimeric studies.

Beyond these various restrictions, two sets of guidelines for human embryonic stem cell research—one from the U.S. National Academies and the other from the ISSCR—influence the conduct and oversight of chimeric research in the U.S. Although similar in many ways, the guidelines are not identical and only the ISSCR guidelines have been recently updated, creating the potential for uncertainty and variation.

Procedurally, both sets of guidelines recommend that institutions conducting hPSC research create specialized oversight committees to review and oversee various subcategories of the research, including studies in which hPSCs are inserted into nonhuman animal embryos or post-natal nonhuman animals. Though much of the research this Special Report addresses falls under the purview of these oversight committees, not all chimeric research involves the use of hPSCs.[81]

Substantively, the two sets of guidelines stress the need for consent from human cell donors to use of their biological materials in research, a requirement that can go beyond the consent requirement imposed by the federal regulators and may include obtaining explicit consent from donors to the transfer the their cells (or cells derived from the donor's cells) into nonhuman animals.[82]

The guidelines also direct oversight committees to focus their review on studies in which human cells could enter the nonhuman animals' central nervous system, especially their brains, although they differ on exactly what the committees should consider. The National Academies' 2010 guidelines require oversight committees to consider "the consequences of the human contribution to the resulting chimeras." They call for a strong scientific justification where studies involve transplanting hESCs or their derivatives into adult nonhuman animals if there is a possibility "that the human cells could contribute in a major way to the brain of the recipient animal," and ask oversight committees to consider "any functional contributions to the brain" of nonhuman animal fetuses that are allowed to develop into adult nonhuman animals.[83] No more specific guidance is given regarding levels of human cell concentration that would and would not be acceptable, how functional impact should be identified, or how much can be permitted, leaving each oversight committee to draw these lines. The ISSCR 2021 guidelines instead recommend that research where human stem or neural cells are transplanted into the central nervous systems of nonhuman animals be reviewed by IACUCs supplemented by "reviewer expertise in stem cell or developmental biology."[84] They provide little specific guidance on how to evaluate whether such research should be allowed to proceed or not.

To address the concern that a nonhuman animal containing human cells might generate human gametes, the 2010 National Academies' guidelines prohibit the breeding of

any nonhuman animals into which hPSCs have been introduced "such that they could contribute to the germ line."[85] The 2021 ISSCR guidelines contain a similar constraint, but neither set of guidelines identifies the basis for this particular rule or offers specific guidance on how oversight committees should determine when a particular study poses this risk.

Regarding research with nonhuman primates, the 2010 revision of the National Academies' guidelines recommended additional review for studies involving nonhuman primates at any stage of fetal or postnatal development and includes a specific rule against research in which hESCs are introduced into nonhuman primate blastocysts. Again, the reasoning is not spelled out but it may be because in such studies it is not known or possible to control where human cells will concentrate in the developing nonhuman primate embryo and therefore it is theoretically possible that a nonhuman primate with a lot of human brain cells or a lot of human germ cells could be born. Contrast this rule with the 2021 ISSCR guidelines, which recommend specialized review of such studies.

BOX 5:

RECOMMENDATIONS [collated list]

1. Scientists, bioethicists, journalists, and others writing about chimeric research should seek to use precise and accessible language that clarifies rather than obscures the ethical issues at stake. In particular, we discourage use of the nouns “chimera” and “humanization”.
2. Ethical and policy analysis as well as governance and oversight of chimeric research should focus on the welfare of any nonhuman animals involved in such studies. Animal welfare is a primary ethical issue and should be a focus of ethical and policy analysis as well as governance and oversight of this research.
3. Scientists, scholars, and other stakeholders should together undertake a focused analysis of what it means for chimeric studies to have a sufficiently strong scientific justification for the proposed use of nonhuman animals.
4. Researchers conducting chimeric studies with nonhuman animals should systematically assess the behavior of their nonhuman animal subjects so that novel changes can be detected, monitored, and reported, including behavioral changes that might indicate novel or unexpected forms of pain, suffering, or lack of flourishing potentially caused by the presence of human cells, especially in the nonhuman animal’s brain or central nervous system.
5. Bioethicists, journalists, and others writing about chimeric research should contextualize chimeric studies within ongoing debates in ethics, science, law, and society about the moral and legal status of nonhuman animals and the morality of using them in research. Developments in these debates may impact chimeric research, and vice versa.
6. Opposition to chimeric research based on concerns about the use of human embryonic or other stem cells in such research, or about human integrity and dignity, should not warrant blanket prohibitions on chimeric research. Nevertheless, respect for the individuals who hold those views may motivate governance approaches that empower people to decide in an informed way whether to donate their cells to such studies.
7. Within institutions, oversight committees that review chimeric studies should establish channels of communication and consider sharing expertise, perhaps by sharing members and/or staff. In addition, procedures for communication between committees should be developed so that committees can consult each other on matters of overlapping interest. At the institutional level, institutions should have mechanisms for tracking research portfolios involving chimeric research so that they can routinely assess the challenges posed by this research as well as any gaps in oversight. Institutions can then proactively decide whether these gaps are acceptable, whether existing

oversight committees should assume responsibility, or whether a new process/committee is needed.

8. There should be a regularly convened national forum where representatives from U.S. research institutions can discuss ethics, governance, and oversight challenges pertaining to chimeric research (whether in the context of larger discussions about other areas of science or as a standalone topic) including issues related to the welfare of nonhuman animals containing human cells.

9. Scientists, funders, research institutions, research advocates, and journalists should provide to the public clear information about chimeric research and the various scientific reasons for conducting specific studies. They should avoid using technical scientific language and references (either in writing or with visuals) to mythological chimeras. Visuals that depict realistic in vitro and in vivo chimeric research would be more helpful in clearly communicating to the public the nature and purposes of the research.

10. In recognition of the importance of public communication about chimeric studies, funders should provide financial support to cover collaboration between researchers and communications staff. Research institutions should assert the value of effective lay communication for continued scientific progress by recognizing such efforts when granting tenure and supporting access to a robust communications staff. Academic journals can contribute to this endeavor by allowing or requiring that lay summaries, other documents, or video abstracts appear with a published scientific article. With more readily available lay language, journalists and their editors should endeavor to represent the science as clearly, simply, and accurately as possible.

BOX 6:

ABOUT THIS PROJECT

The NIH-funded project from which this Special Report was developed was led by a research team comprised of bioethics experts at The Hastings Center (HC) and Case Western Reserve University (CRWU). The HC/CRWU research team undertook a mixed-methods research project that included:

1. Reviewing existing guidelines, recommendations, laws, regulations, funder requirements and academic literatures (e.g., in stem cell science, bioethics, and animal studies) pertaining to research with human stem cells and nonhuman animals;
2. Conducting 35 audio-taped in-depth interviews with relevant scientists and members of relevant oversight committees to better understand the strengths and challenges of current oversight approaches for research with human stem cells and nonhuman animals;
3. Analyzing a sample of the more than 20,000 public comments the NIH received in response to the agency's proposed funding policy for certain types of human stem cell research with nonhuman animals; and
4. Creating an interdisciplinary Work Group composed of: scientists engaged in human stem cell research with nonhuman animal embryos and post-natal nonhuman animals; members of relevant oversight bodies (primarily embryonic stem cell research oversight (ESCRO/SCRO) committees and institutional animal care and use committees (IACUCs)); and academic researchers in philosophy, law, bioethics, and nonhuman animal studies. The workgroup undertook an interdisciplinary analysis to investigate the motivating factors for the project and to identify inconsistencies and uncertainties about ethical, conceptual, and oversight dimensions of research with human stem cells and nonhuman animals.