Journal of Law, Medicine & Ethics (2026), **54**, 1, 1–9
doi:10.1017/jme.2025.10210

CAMBRIDGE UNIVERSITY PRESS

Independent Articles

Balancing Progress and Precautions with Emerging Biotechnologies: Evaluating the Process of Gene Therapy Research Becoming "Normal"

Stephanie Solomon Cargill[†]
Alden March Bioethics Institute, Albany Medical College, United States

Abstract

In recent years, we have seen an immense expansion in recombinant DNA, especially in its use in gene therapy applications. Throughout its history, the United States set up several mechanisms of national safety and ethical oversight for rDNA to ensure that we proceeded with its use appropriately. As our knowledge and experience with it grew, there has been increasing pressure to decrease the oversight and monitoring requirements for its use. In 2019, the National Institutes of Health amended the NIH Guidelines for Research Involving Recombinant DNA Molecules eliminated three national mechanisms for guidance, monitoring, and review of this biotechnology. Four years later, we revisit these changes and their implications for a current emerging biotechnology: xenotransplantation. By better understanding the motivations for these mechanisms and analyzing the test case, we argue that these changes have worrisome implications for our ethical oversight of emerging biotechnologies both in the realm of gene transfer technologies and beyond.

Keywords: Gene therapy; Biotechnologies; Recombinant DNA Advisory Committee (RAC); Institutional Review Boards; Institutional Biosafety Boards

Part I

Normally, amendments to federal guidelines do not garner much attention. The 2019 Amendment to the *NIH Guidelines for Research Involving Recombinant DNA Molecules* (hereafter referred to as *NIH Guidelines)* would not, at first glance, be worthy of note. But in spite of its run-of-the-mill appearance, this amendment signified the culmination of an innovative and controversial decades-long federal engagement with a new biotechnology. Recombinant DNA (rDNA) is a technology which involves using enzymes or other laboratory techniques to manipulate or isolate DNA (or RNA) to create genes with new functions.[1] Since it emerged as a possibility in the 1970s, researchers, the government, and the public have been grappling with how to engage its possibility and risks appropriately. Through debates, negotiations, and learning from mistakes, three mechanisms were developed that characterized how rDNA research could be safely and appropriately conducted in the US. The 2019 Amendment to the *NIH Guidelines* eliminated all three of these mechanisms.

In this paper, I argue that some version of the three mechanisms removed by this Amendment should be reinstated and put in place as ethical guidance for all emerging biotechnologies.[2] These mechanisms should include: flexible national guidelines with widespread buy-in (not regulations)[3] which provide ethical and procedural guidance for local review to protect both participants, close contacts, and the public as the technology develops; a diverse, transparent, standing national committee which provides scientific and ethical deliberation and consultation to local review; and a national database of clinical trials using the emerging biotechnology to aggregate adverse events and unintended consequences. A version of each of these mechanisms was developed to engage the emergence and development of recombinant DNA (rDNA) and should remain in place as mechanisms for ethical oversight for all emerging technologies.

I will make this argument by showing in Part II how these three mechanisms for rDNA research developed to address distinct challenges and insights as this biotechnology evolved from laboratory science to clinical trials. In Part III, I will show how a currently emerging biotechnology, xenotransplantation, illustrates these shared challenges and insights and the common need for these three mechanisms. I will also show how these needed mechanisms are not currently in place. I will conclude with a demonstration of how these different mechanisms are needed to generate ethical guidance of current novel uses of rDNA (like in utero and germline uses) as well as for other emerging biotechnologies (like xenotransplantation and others).

Part II: History of Recombinant DNA Oversight

When scientists first realized they could manipulate DNA and RNA within cells, many among their ranks urged caution. This new technology held the potential to revolutionize fields as varied as industry, agriculture, environmental science, and medicine, and in the latter to treat and even cure some of the most severe and tragic ailments that human beings have encountered. This technology also posed unknown potential risks of cancer or infectious diseases to those who worked with it in laboratories, as well as to the

[†]deceased.
Email: gligorn@amc.edu

Cite this article: S.S. Cargill. "Balancing Progress and Precautions with Emerging Biotechnologies: Evaluating the Process of Gene Therapy Research Becoming 'Normal'," *Journal of Law, Medicine & Ethics*, **54**, 1 (2026): 1–9. https://doi.org/10.1017/jme.2025.10210

© The Estate of Stephanie Solomon Cargill, 2026. Published by Cambridge University Press on behalf of American Society of Law, Medicine & Ethics.

https://doi.org/10.1017/jme.2025.10210 Published online by Cambridge University Press

environment if released from the confines of the laboratory. Finally, it posed unknown potential risks to close contacts or progeny of those exposed to it.

In 1974, the National Academy of Science (NAS) established a scientific committee to review the state of knowledge about the laboratory and environmental risks of rDNA research as well as the methods of addressing those risks, later referred to as Asilomar I. Among the community of scientists engaged with this project, there was no acknowledgment in this remit of the larger social, ethical, and legal issues posed by this emerging biotechnology.

Asilomar I issued a summary letter, published in *Science*, that made three important recommendations: (1) call a temporary moratorium on rDNA research that should be lifted only under stringent safety oversight conditions; (2) establish a national-level advisory committee (at the NIH) to evaluate the risks of rDNA, develop procedures to minimize those risks, and devise guidelines for work with rDNA; and (3) to hold an international meeting to discuss the appropriate approach to conducting research with rDNA.[4]

In late 1974, the National Institutes of Health (NIH) responded by assembling the first generation of what would become known as the Recombinant DNA Advisory Committee (RAC). It appointed members with relevant scientific expertise, using the NIH model of recruiting for scientific study sections to review grants, and it was set up as a governmental advisory committee to give advice to the NIH director in matters related to this technology.[5] This "first generation" RAC would evolve through the years many times. Meanwhile, the NIH contracted the National Academy of Science to put together an international conference of the leading minds in the emerging field of rDNA science. In February 1975, the "Asilomar Conference on Recombinant DNA Molecules"[6] took place, attended by US scientists nominated by the NIH as well as scientific academies in 11 industrialized countries.[7] This second Asilomar conference's charge was to come to a consensus on what safeguards should be in place in order for the self-imposed moratorium to be lifted. The result of this conference was the recommendation to lift the moratorium and cautiously conduct rDNA research under stringent laboratory safety rules as well as local and national oversight conditions, outlined in a summary letter.

The very next day, the summary letter from Asilomar II was handed over to the newly appointed director of the NIH, Donald Fredrickson. Leaders at the NIH quickly recognized three important insights: (1) the public should be consulted regarding any rules governing this novel biotechnology, (2) any rules governing this technology must remain flexible as the evidence evolved, and (3) the national governance of this novel technology should remain at the NIH.[8] This last claim was justified by the fact that the NIH had a wealth of scientific expertise to assess novel technologies, it was answerable to the government in the form of Congressional oversight, and it could enforce compliance with guidelines through fiscal pressures upon a large proportion of those conducting this research without ensconcing legal regulations that were difficult to change.[9]

In the hands of the NIH, the Asilomar II letter became a proposed draft of the *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules*, and leaders at the NIH worked it through a unique process that gave it a quasi-legal status within the government. While the NIH could not issue regulations, it wanted these guidelines to have more authority than "mere" guidelines normally issued by federal agencies that serve as strong suggestions or recommendations but hold no authority at all. In order to do so, the NIH director set up a "public meeting" about the *NIH Guidelines*. He ran it through both a diverse[10] and publicly available Director's Advisory Committee (DAC) and the *Federal Register* public comment process. The RAC revised and refined the *Guidelines* in response to this feedback, and the final version was published in the *Federal Register* on June 23, 1976. Meanwhile, the NIH director also called together the leaders of 16 federal regulatory agencies — as well as the National Science Foundation, Departments of Agriculture, Justice, and Defense, and NASA — in order to gain agreement to abide by the *NIH Guidelines*, which they did in late 1976.[11]

The newly revised and approved *NIH Guidelines* specified how rDNA research would be overseen at both the national and local level. At the national level, the RAC was changed from an advisory body to a reviewing body with the authority to approve or reject protocols based on their scientific, ethical, and social merits. At the local institution level, the *NIH Guidelines* required Institutional Biosafety Committees (IBCs) to provide biosafety review for laboratory personnel, the public, and the environment.[12] Since initial rDNA research took place exclusively in laboratories, the content of the *NIH Guidelines* provided the RAC and IBCs with a review framework to focus its considerations on safety concerns for laboratory workers and the public (perceived as environmental threats). But as there was increasing hope that this technology would soon be applied to humans, the concerns about safety would soon move beyond the laboratory.

In 1978, the first major evolution of the RAC occurred. Reflecting the questions posed to the RAC — which were not entirely scientific in nature but also legal, social, and ethical — secretary of the Department of Health, Education, and Welfare Joseph Califano required that the RAC diversify its membership to at least a third nonscientists. In response, the RAC was expanded from 11 to 25 members. In addition to diversifying, this "second generation" RAC also took steps to increase its transparency and accountability to the public by creating an openly accessible archive of all its documents. Each of its meetings were publicly announced and public, with proceedings published in the *Federal Register*. These published proceedings then elicited public comments, with the NIH Director reviewing and answering each comment. This unique approach to "public deliberation" was deemed appropriate for the types of social and ethical questions posed by novel biotechnologies.[13]

In 1980, a geneticist at UCLA named Martin Cline attempted to treat two patients with severe beta-thalassemia with genetically modified cells without any permission or approval, which violated both the *NIH Guidelines* as well as federal regulations for human subjects research. Shortly thereafter, leaders of Christian and Jewish communities came together to write a letter to President Jimmy Carter about their religious, moral, and ethical concerns about human "genetic engineering." As a result, in 1982 President Carter convened the "President's Commission for the Study of Ethical Problems in Biomedical and Behavioral Research" to consider the ethical use of recombinant technologies for "genetic engineering" in humans. President Carter's commission culminated in the report *Splicing Life* that called for the establishment of an interagency committee comprised of scientists and laypersons to oversee and educate about human gene therapy (HGT) trials or expand the RAC's oversight role to intentionally encompass not only safety but also ethical issues. It emphasized that this group should be diverse and not dominated by scientists.[14]

Four days later, then-Representative Al Gore convened congressional hearings on the topic of genetic engineering, which also concluded that there should be a national-level deliberative or

https://doi.org/10.1017/jme.2025.10210 Published online by Cambridge University Press

regulatory body with as little conflict of interest as possible with the promotion of the research to review the safety and ethicality of HGT research. At the time, the RAC was seen as the place to fulfill both of these calls to action.[15]

Also in response to Al Gore's hearings, in 1984 the (later defunded) Office of Technology Assessment (OTA) released a paper called *Human Gene Therapy*, which concluded that there was a moral consensus between civic, religious, scientific, and medical groups in US society that *somatic* HGT, applied to severe genetic diseases, is acceptable as an analog and extension of current methods of therapy.[16] Aligned with this consensus, in 1985 the RAC completed an initial draft of a document entitled "Points to Consider in the Design and Submission of Somatic Cell Human Gene Therapy Protocols," which articulated both the content and the process of review of somatic HGT research at the federal level with the RAC, and the local level with institutional biosafety committees (IBCs) and institutional review boards (IRBs). It echoed the Office of Technology Assessment paper by emphasizing societal acceptance of performing somatic HGT, while remaining resistant to endorsing clinical trials of germline HGT or in utero HGT.

"Points to consider" expanded the existing *NIH Guidelines*' concerns about risks to laboratory personnel to focus on the safety risks to research participants (the local purview of IRBs), their close contacts (the local purview of IBCs), and their progeny (IRBs currently take this as their purview) as well. In addition, it expands the concerns of the reviewing committee to the "scientific, safety, medical, or social issues" of the protocol, not merely the scientific and safety concerns.[17] This document was adapted and adopted by the *NIH Guidelines* soon after as a portion of the document called Appendix M, and provided guidance for both the RAC and local IBCs in how to review HGT trials in light of ethics and public health.

The expansion into clinical trials led to shifts in oversight. When rDNA research started to be applied directly to humans in clinical trials, it didn't leave the purview of the NIH, but it entered the purview of an arguably stronger governmental body, the Food and Drug Administration (FDA). The overlapping jurisdiction and increasing clinical applications of rDNA research led to cooperation and discussion between the NIH and FDA regarding the appropriate federal oversight and monitoring of HGT research. The FDA regulates all new drugs or devices no matter the funding source, and human gene therapy research involves both cellular and gene therapy products as well as novel devices. Unlike the publicly funded NIH that reviews research for the purpose of contributing to fundamental knowledge and applying it to improve the public's health,[18] the FDA reviews clinical trials with the purpose of ensuring the quality of the scientific evaluation is adequate to determine whether the drug is safe and effective for marketing to the public.[19] Due to their different funding mechanisms and purposes, the NIH is both more transparent and less conflicted with industry than the FDA, which has a closed process and is significantly funded by user fees from the private industry it reviews.[20]

In 1986, the FDA asserted jurisdiction over HGT products while it was still willing to share some regulatory roles with the NIH.[21] In 1991, it issued its own "Points to Consider," although unlike the NIH document that examined the social, ethical, and legal landscape of HGT and gave specific guidance on the review of issues of public health, this document focused narrowly on the FDA's technical interests in the safe manufacturing of somatic cell and gene therapy.[22] It also didn't include discussion of the ethical concerns or public health considerations outside of some brief offhand statements. This narrower scientific focus is appropriate, as the FDA doesn't include publicly accessible or publicly inclusive mechanisms in order to have the expertise and buy-in to discuss these broader topics like the RAC at the NIH does.

At the same time that regulatory oversight was shifting to the FDA, the number of protocols involving rDNA and the pressure to expedite them became more intense, especially from AIDS activist groups. Meanwhile, many of the emerging protocols were variations and extrapolations of early studies, so they did not raise novel safety or ethical issues. In response, throughout the next couple of years the RAC looked for responsible ways to expedite their reviews by focusing only on those that "represent a significant degree of departure from familiar practices" or "could lead to the formulation of significant new policy." But they always maintained the importance of the RAC's unique existence as the "sole open forum in which to air general issues of ethics and public safety" of novel biotechnologies. They also requested that proprietary restraints on investigational new drug (IND) applications (maintained for publication and patenting purposes) be lifted so that public discussion of the novel issues posed by these technologies could be raised.

In 1997, an amended version of the *NIH Guidelines* reduced the authority of the RAC from a reviewing body back to an advisory role for only controversial studies, thus ceding all regulatory authority to the narrowly set mission of the FDA at the federal level, and leaving all of the assessment of ethics and public safety to the IRBs and IBCs at the local level. That same year, the newly passed Food and Drug Administration Modernization Act of 1997 required the NIH to create a public information resource on certain clinical trials regulated by the FDA, called ClinicalTrials.gov, although it was required of few studies and included meager information about them.[23]

The consistent process of reducing the RAC oversight of HGT research likely would have continued but for the tragic death of Jessie Gelsinger, a "healthy"[24] volunteer in an ornithine transcarbamylase (OTC) deficiency gene therapy trial in 1999. Investigations into his death revealed that the joint NIH-FDA process had shown weakness in trial oversight and transparency, especially in the domain of conflicts of interest and sharing of adverse events across trials. Researchers appeared to be disinclined to share as much data with the RAC as with the FDA due to the higher confidentiality measures of the latter, while it was the former that publicly assessed adverse events data across trials making it useful to prevent participants from being exposed to risks known from other studies using similar mechanisms.[25] In response to the issue, the NIH created the Genetic Modification Clinical Research Information System (GeMCRIS), although it did not become operational until 2004. A joint FDA/NIH venture, HGT researchers were required to register their clinical studies with GeMCRIS. The database included trial information about medical conditions under study, institutions where the trials were located, and investigators of trials (like clinicaltrials.gov), but also included types of HGT vectors and other details of the adverse events using a secure electronic interface.[26]

With the RAC limited to full (advisory) review of only controversial protocols, local oversight bodies took on more and more responsibility for the oversight of HGT protocols, controversial or not. IBCs, as mentioned above, are charged with protecting "laboratory personnel, the public, and the environment." While they traditionally focused on laboratory safety, with the advent of HGT, their charge moved out of the laboratory and into the clinic. rDNA in clinical settings poses risks not only to laboratory personnel, but also to clinical staff, close contacts of research participants, and the public, all of whom are ostensibly under the purview of

https://doi.org/10.1017/jme.2025.10210 Published online by Cambridge University Press

IBCs. They were, until recently, guided in this expanded review of the public health risks of HGT, such as viral shedding, by Appendix M, which delineated public health considerations of clinical trials (Appendix M-II-B-4) that are not mentioned in any of the prior sections of the *NIH Guidelines*. By administering the criteria from Appendix M in their reviews, they were able to evaluate the clinical (as opposed to laboratory) biosafety risks of HGT.[27]

HGT studies, as human subjects research, also require review by IRBs. This requirement applies to any research funded by the NIH, and more frequently for industry-sponsored studies, under the auspices of FDA regulations. IRBs are charged with the protection of participants in research studies, and therefore must review and approve both the protocol as well as any participant-facing materials to ensure that participants make an informed, voluntary choice to participate in research that has a fair risk/benefit ratio. Their scope is notably limited to protecting the trial participants and does not extend to broader ethical concerns such as long-term applications of the knowledge or public health concerns considered by the RAC and IBCs respectively.[28]

In spite of this increasing dependence on their review, IRBs and IBCs often lacked local expertise on especially the more novel and innovative technicalities of HGT trials. Fortunately, they could rely on the expertise of the RAC, either because it had provided prior review, or because they could consult the RAC when they encountered unprecedented studies without sufficient guidance.[29]

In 2018, in the ironically titled, "The Next Phase of Human Gene-Therapy Oversight" NIH director Francis Collins and FDA director Scott Gottlieb jointly announced the need to "safely expedite progress" by eliminating almost all HGT oversight at the NIH.[30] While there had been calls to reduce and eliminate aspects of rDNA research oversight in the past, with the full support of the both directors, this oversight came to an end. The 2019 Amendment to the *NIH Guidelines* made three important changes:

- It eliminated the RAC entirely as an advisory/review body.
- It eliminated the requirement in the *NIH Guidelines* that all clinical trials must register and report to GeMCRIS.
- It eliminated Appendix M from the *NIH Guidelines* which contained the "Points to Consider" guidance for the special review of HGT trials.

The justification for the change provided by the NIH and FDA directors (among others[31]) was that HGT was adequately reviewed by the FDA at the national level, and IRBs and IBCs at the local level. Future emerging biotechnologies would be assessed by a newly born replacement, Novel and Exceptional Technology and Research Advisory Committee (NeXTRAC), established in 2019. GeMCRIS was obsolete because a national database of clinical trials was achieved by the increasingly robust clinicaltrials.gov. Finally, Appendix M was not required because *NIH Guidelines* and IBCs should move their focus back to laboratory biosafety.[32]

While these justifications appear reasonable, they too swiftly overlooked the important and unique role that the NIH infrastructure of guidance, oversight, and monitoring played in engaging emerging technology responsibly. Aspects of the RAC, GEmCRIS, and the *NIH Guidelines* Appendix M need to be in place for all emerging research, and are not currently in place with NeXTRAC, clinicaltrials.gov, and the *NIH Guidelines* without Appendix M.

In the next section, I will argue that without some version of the three mechanisms eliminated by Appendix M, important gaps emerge in the areas that made them crucial engagements with the evolution of novel biotechnologies. This infrastructure requires neither reinstating the RAC nor assuming that recombinant DNA research is entirely "novel," but does require understanding the multiple roles this infrastructure served that should be seen as neither unnecessary nor redundant.

Part III

While a meaningful absence in oversight is difficult to prove empirically until or unless a scandal occurs, a reasonable litmus test for how well our current (post-2019 Amendment) national system engages emerging technologies is to evaluate how well it engages with a test case: xenotransplantation. Researchers have been studying the possibility of xenotransplantation — the use of live animal cells, tissues, and organs in the treatment or mitigation of human disease — in the preclinical space for decades. Early forays into human applications are much older than research with rDNA (documented as early as the seventeenth century), reflecting both the technical accessibility of animals as well as the more widespread medical need for organs that called for their use. In the US, doctors trying to save their dying patients turned to nonhuman primate kidneys, livers, and hearts as early as the 1960s.[33] In the 1990s, while there were yet no ongoing US clinical trials of solid organ xenotransplants, several clinical trials of tissue xenotransplants for treatment of AIDS and Parkinson's disease were underway.[34]

But the scientific and medical community recognized that clinical trials involving xenotransplantation were on the horizon, bringing with them numerous scientific, ethical, and public safety questions. In a surprising show of federal support, in 1995 the NIH, FDA, CDC, and the Department of Defense as well as two foundations sponsored the Institute of Medicine (IOM) to convene an "expert committee" consisting of clinicians, transplant surgeons, immunologists, specialists in infectious diseases, and social scientists. The committee participated in a 3-day workshop with 43 speakers and 200 participants, including members of diverse stakeholder groups. This process culminated in *Xenotransplantation Science, Ethics, and Public Policy*, published in 1996 (1996 Report). This report, much like the *Splicing Life* report issued for HGT research by the President's Commission in 1982, reviewed the current science, public health risks, and ethical and public policy issues of xenotransplantation. Also in 1995, the International Xenotransplantation Association (IXA) was established with the mission to promote xenotransplantation as a "safe, ethical, and effective therapeutic modality."[35] This organization holds annual meetings, started a journal in 2000, and has its own ethics committee.

Shortly after the 1996 Report was issued, the Department of Health and Human Services (DHHS), which encompasses both the FDA and the NIH, proposed draft National Guidelines about xenotransplantation. In an impressive collaboration between the CDC, FDA, Health Resources and Services Administration (HRSA), and NIH (among others), this draft was created and published for public comment in the Federal Register. Meanwhile, echoing the moratorium the Asilomar I scientists put on rDNA research, the FDA placed all clinical trials using pig xenotransplantation products on hold pending the development of appropriate safety measures and informed consent documents.

Shortly thereafter, DHHS began sponsoring public workshops that engaged scientists and the public (both US and international) to gain their insights on an appropriate federal policy towards xenotransplantation. Out of these workshops came revisions to the draft in response to the "broad consensus" surrounding the necessity for public awareness and participation in the development

https://doi.org/10.1017/jme.2025.10210 Published online by Cambridge University Press

of any public health policies for xenotransplantation as well as the "strong support" for a national advisory committee "not only to facilitate analysis and discussion of the scientific, medical, ethical, legal, and social issues raised by xenotransplantation, but also to review and make recommendations about proposed clinical trial protocols."[36]

This mechanism initially took the form of a DHHS Secretary's Advisory Committee on Xenotransplantation (SACX). This committee was established to "consider the full range of complex issues raised by xenotransplantation, including ongoing and proposed protocols" as well as "provide a forum for public discussion of issues when appropriate."[37] In spite of the widespread recognition of the importance of such a mechanism, it only appears to have existed until 2005. It is difficult to find evidence of this committee's existence or composition, and its sole product appears to be a draft report only retrievable from the IXA website.[38]

In spite of this thoughtful preparation, clinical research using xenotransplantation continued to be delayed due to scientific infeasibility. This changed coincidentally thanks to advances in rDNA techniques with CRISPR in 2012. Genetic modifications in pigs made xenotransplantation with pig organs without zoonotic transmission possible. In 2019, a macaque survived for more than a year with a kidney xenotransplanted from a genetically altered pig. In 2021, the University of Alabama successfully transplanted a genetically modified pig kidney into a brain-dead human. Using the FDA's expanded access mechanism that allows treatment with investigational products in life-threatening circumstances with no alternatives, pig hearts and kidneys began to be transplanted into living humans with limited success in 2022. As of 2024, there were still no clinical trials (yet) for pig kidney xenotransplantation.[39] This seems the right time to evaluate how the US system (after the changes implemented in 2019) is prepared for the emergence of xenotransplantation, a biotechnology that poses unknown and novel risks to participants as well as broader ethical, social, and public safety issues.

Elimination of the RAC, Formation of NExTRAC

The primary argument for eliminating the RAC was that it was rooted less in the need for an ethical review of any particular technology (in this case human rDNA research), and more in the need for ethical and public safety consideration of *any* emerging biotechnologies that posed unknown and novel risks and benefits. In the almost fifty years since the Asilomar I conference argued for the creation of a national advisory committee, rDNA technologies have been much better understood and less in need of national scrutiny at a high level, and other technologies have emerged that are more deserving of this attention. Thus, the argument goes, the RAC was not "eliminated" by the 2019 amendment, but rather "renamed" and "repurposed" as the newly created NExTRAC.

NExTRAC was established in 2019 and is intended to address the scientific, safety, ethical, and social issues associated with any emerging biotechnologies.[40] Based on documents that led to its establishment, NExTRAC is intended to have two functions: (1) horizon scanning to prospectively identify emerging biotechnologies, and (2) determining whether, how much, and what kind of deliberation is needed about a particular emerging biotechnology.[41] This deliberation could then be conducted by members of NExTRAC, a working group established by NExTRAC, and/or through other mechanisms such as public engagement strategies. So how have these two functions worked in the case of xenotransplantation?

First, one would expect that in its six years of its existence, NExTRAC's horizon scanning would perceive xenotransplantation as an obvious target. In the 2020 *Report to Establish a NExTRAC Framework*, it states that the qualities of a biotechnology that should prompt visibility in horizon scanning include "likely widespread use, insufficient regulation, unknown risks and implications, uncontainable or irreversible impacts, increasing health inequities, uneven distribution of impacts, and lack of awareness and consent."[42] Without much argument, one can see how xenotransplantation would satisfy most, if not all, of these criteria. If seen as a source of safely transplantable organs, it would see very widespread use. As a transplant, like gene therapy it is a permanent choice (irreversible impacts). Because it requires extensive resources both from providers and patients, it is likely to increase health inequities and have an uneven distribution of impacts. It raises many broader societal issues surrounding animal ethics and religious priorities. Finally, many have already documented the challenges xenotransplantation poses to the consent process, both with transplant recipients and their close contacts.[43]

Since its establishment in 2019, NExTRAC and the NIH director's horizon scanning has culminated in four working groups, each ostensibly devoted to a charge provided by the NIH director. These working groups demonstrate the topic areas where NExTRAC has focused its energies, and their reports provide the content to the public meetings that are held at most twice per year. These working groups are: (1) the Working Group to establish a NExTRAC framework (culminating in the report cited above); (2) Data Science and Emerging Technology; (3) Gene Drives in Biomedical Research; and (4) Engaging the Public as Partners in Clinical Research. The first three have issued final reports on the topics in question.[44] The last represents what is apparently NExTRACs sole charge from August 2023 until summer 2026, which is to establish a working group to develop a vision and framework for including public voices in the design and planning of NIH-funded clinical research, as well as widespread dissemination of study findings.[45]

It is safe to say that if we are assessing NExTRAC's horizon scanning function, the litmus test of xenotransplantation has failed. This could be because either xenotransplantation was missed by NExTRAC's horizon scanning function, or that it only has the bandwidth to take up one charge from the NIH director at a time, and in this rarified space the NIH director has not chosen to devote NExTRAC resources toward this particular emerging technology for scrutiny. Nonetheless, NExTRAC is either unable to perceive xenotransplantation as a significant emerging technology worthy of its attention, or it doesn't have enough time or resources to give it the attention it deserves. Although the RAC was never meant to serve this function, if NexTRAC is supposed be the national level radar to engage with emerging biotechnologies, this signaling seems to have failed.

The second function of NExTRAC is to determine whether, how much, and what kind of deliberation is needed about a particular emerging biotechnology. Although NExTRAC was silent on this issue, both the 1995 Report and the 2001 PHS Guidelines were explicit. As discussed above, they called for a national level advisory committee composed of experts and stakeholders to provide ongoing deliberation and consultation as the research moves forward. This sounds more like an established committee like the RAC than the short-term working groups of NExTRAC with a "charge" that culminates with a "report" at the end of a predetermined period of time. It was also learned from the history of the RAC that the

https://doi.org/10.1017/jme.2025.10210 Published online by Cambridge University Press

deliberative body would need to evolve through time to be appropriate to the evolution of the biotechnology. And this evolution was stabilized by the coevolution of a flexible guidance document that both defines the role and deliberations of the committee while also being defined by that committee. The 2001 PHS Guidelines could have served this role.

Also unlike NeXTRAC, the RAC had the mission to provide education and consultation for IRBs and IBCs who were reviewing this research at the local level. With its diverse expertise and history of reflecting on ethical questions about novel science, the RAC served as a crucial source of information and consultation for these local review mechanisms when issues arose in individual studies that were without precedent or guidance, including but not limited to third-party/close-contact risks. As xenotransplantation poses similarly complex ethical and scientific questions, and similarly poses third party/close contact risks, IRBs and IBCs will likely need analogous consultation and guidance on the technical and ethical issues of xenotransplantation.[46]

Those who would suggest that NExTRAC is a legitimate replacement for the RAC need to address these apparent failings of NeXTRAC to fulfill its first function, and arguably even to be able to fulfill the second one with its current approach. First, NExTRAC needs the funding and support to adequately serve its horizon scanning function and to make these "scans" public. Then, even if it cannot itself act on the emerging biotechnologies because of limited resources or because the NIH director does not charge it to, at least the information about what to be on the lookout for, and why, will be made available.

Second, while NExTRAC is not constituted nor supported to serve as an ongoing, stakeholder-engaged, government-endorsed advisory committee, it should serve as the launching pad to start forming them. When biotechnologies like xenotransplantation emerge on the horizon, they need to start doing the legwork to see what has already been done to articulate the type of deliberations and stakeholders needed (like the 1996 Report, the Public Health Service Guidelines, and the Secretary's Commission), or start forming an advisory committee from the ground up with the expertise and input to engage that particular technology. Among other things, this national committee would need to: (1) have diverse stakeholder input including, but not dominated by, scientists; (2) have a flexible role to either advise or review (or both) depending on the state of the field; (3) engage broad legal, social, and ethical issues of the emerging biotechnology; (4) engage potential public health risks of the emerging biotechnology; (5) have the ability to lift proprietary IND constraints around studies (if justified) for review of novel uses; and (6) have the mission to educate and engage the broader society, especially focusing on local review bodies (both IRBs and IBCs). These six functions were learned to be crucial from the history of rDNA research, and without the RAC or something like it, are lost.

Finally, NeXTRAC could also function as the mechanism to determine when an advisory committee has reached its terminus. As we saw with rDNA, there are numerous pressures to lessen the authority of national oversight bodies such as this, and even more pressure to remove them altogether. It is important that these entities not come to a premature end due to concerns about efficiency of review that underprioritize public safety and ethical concerns. It is therefore necessary to determine explicit and objective criteria for when a special committee has fulfilled its goals, corresponding with the judgment that an "emerging" technology has "emerged."[47]

Elimination of GeMCRIS, Use of ClinicalTrials.gov

The 2019 Amendment to the *NIH Guidelines* eliminated the requirement for registering and reporting HGT trials to GeMCRIS. This change was justified by the argument that clinical trials and their corresponding information already are required to be registered on the publicly accessible clinicaltrials.gov. Thus, the argument goes, having a database solely for recombinant DNA research was redundant and burdensome to researchers.

In order for IRBs and IBCs to do their job at the local level, they need to know the most up-to-date safety and risk information that is relevant for the trials they review. As discussed above, GeMCRIS' initial formation was motivated by: (1) the inconsistent reporting of serious adverse events by sponsors to different agencies; (2) the concern for protecting confidential commercial information; and (3) the need to prevent alarm to the public from sharing raw, unanalyzed, adverse event data with them.[48] In response, GeMCRIS balanced transparency and security by gathering detailed data about HGT clinical trials — consistent with FDA reporting — that included all serious adverse events, but gave access at different levels to different users. Ultimately, the database was able to aggregate all adverse event reports submitted across protocols, and was searchable based on clinical application, vector, transgene, or the nature of the clinical event. This resource was specifically useful to IBCs who may have access to safety data of other sites within multisite trials, but do not have access to safety data from other trials using similar or the same technologies.

This is another aspect of the history of rDNA with direct parallels to xenotransplantation. As shown above, both the 1996 Report and the PHS Guidelines called for a national xenotransplantation database.[49] The PHS Guidelines articulated the purpose of this database: "[to] enable: (a) the recognition of rates of occurrence and clustering of adverse health events …; (b) accurate linkage of these events to exposures on a national level; (c) notification of individuals and clinical centers regarding epidemiologically significant adverse events.; and (d) biological and clinical research assessments."[50] It is noteworthy that the PHS Guidelines, which came out in 2001, did not even mention clinicaltrials.gov.

Even if we concede that HGT transfer studies no longer need this level of scrutiny, the existence of a cross-project database of studies utilizing emerging biotechnologies remains important and useful for researchers as well as regulators. Especially in the early years of an emerging technology, when small studies testing the same approach may be happening simultaneously in different places, it is especially important for the specifics of any adverse events from one study to be shared with other reviewing bodies so that they can inform and protect participants from those same harms. Clinicaltrials.gov could serve this purpose, but it would need to expand its level and type of data available to be of use for it. Or these specialized databases could be temporary, coming into existence and evolving alongside the national reviewing body.

Elimination of Appendix M (National Guidelines for Ethics and Public Safety of Clinical Trials)

The primary argument for eliminating Appendix M was that it was guidance for special oversight considerations of rDNA clinical trials, and there was no more need for special oversight considerations. A secondary benefit would be to focus local IBC review back on laboratory safety (implicitly "where it belongs").[51] As we can see from the recent history of engagement with xenotransplantation, it

https://doi.org/10.1017/jme.2025.10210 Published online by Cambridge University Press

is clear that national guidance to help IRBs and IBCs to engage with broad ethics and public health issues of emerging technologies is called for. While some aspects of Appendix M do read as directed specifically at rDNA research, the general framework is appropriate for review of any emerging biotechnology.

The introduction is an overview of the current national consensus on what uses of the technology are allowed and which are still under national discussion, as well as the focus of a national review of unintentional consequences for vertical (to offspring) and horizontal (to close contacts) transmission. It also discusses the existing process for review and monitoring of studies, including when local and national review are triggered. Finally, it articulates what aspects of research subjected to review and monitoring can be kept confidential.[52] Appendix M then goes on to articulate the information that needs to be submitted for (national and local) review, as well as the details of that review, and then the information that needs to be submitted for (national and local) monitoring. Next it poses scientific questions to guide the review of the specific protocols submitted to them.

In M-II-B-4, "Public Health Considerations," Appendix M asks about the potential benefits and hazards of the research "to persons other than the human subjects receiving the experimental treatment," along with what precautions and measures will be put in place to prevent and mitigate these risks. Like with HGT research, jurisdiction over risks to close contacts is ambiguous with xenotransplantation, shared between the IRB (who is usually concerned primarily with risks to progeny) and IBCs (who have official jurisdiction over public health concerns, including close contacts). The latter responsibility is problematic here, since IBCs have little control over many precautions or mitigations in the clinical realm, such as informational warnings in participant-facing documentation (under IRB rule) or practices to protect research staff (under OSHA). On the other hand, without Appendix M guiding IBCs to ask public safety questions of emerging biotechnologies, it is unclear who would have the responsibility to do so.

Finally, Appendix M goes through human subjects protection and informed consent considerations. These considerations clearly are under the jurisdiction of local IRB review, although with emerging technologies it is unlikely that their membership will have the expertise to know what and how to adequately inform participants, nor what potential risks and harms to be on the lookout for.[53] With HGT research, it took many years for IRBs to have adequate background and experience to know to warn participants of the unique risks of HGT trials, such as: the risk that participation in one HGT trial might exclude them from future HGT trials (due to antibody resistance); that there is no possibility of withdrawal from the HGT, as it remains in the body over time; the corresponding, potentially extensive, length (and importance) of post-trial monitoring, etc. With xenotransplantion and other potential emerging technologies, one would expect that it would take a considerable period of time before IRBs would have easy access to researchers and ethicists with expertise, and even longer before they would have adequate expertise among their membership. Centralizing this expertise for emerging biotechnologies — either as an additional review mechanism to protect human subjects, or as an advisory/educational mechanism — seems an important initial step for all emerging biotechnologies until expertise becomes more widespread.

Appendix M finishes with a section called "Specific Requirements of Gene Transfer Research," which addresses issues particular to that biotechnology, such as: long-term follow-up, request for autopsy, interest of the media and others in the research, and corresponding issues of balancing public transparency and privacy concerns for the early participants in the emerging biotechnology. Again, these seem to be issues *not* specific to HGT, but important concerns for any new biotechnology.

Ultimately, some document that addresses similar issues as Appendix M/Points to Consider should be part of any national guidelines for an emerging biotechnology. Guidelines on these types of issues should be developed using a similar process to the *NIH Guidelines*, namely: publicly transparent, stakeholder involved, interagency approved, and published through the Federal Register. This document would serve multiple purposes: guide/educate the review of the national and local review bodies (IRBs and IBCs), give a stable yet flexible set of guardrails for researchers as the biotechnology develops, and make sure the multiple government agencies are communicating and consistent in their approach to oversight.

Conclusion

The 2019 Amendment to the *NIH Guidelines* made sweeping changes to the way HGT research is guided, reviewed, and monitored in the United States. Since the changes were motivated by the noble intention to remove redundancy without sacrificing oversight protections, it is vital to evaluate whether this intention has been accomplished. By exploring the history of the approaches to oversight as they emerged with rDNA and HGT research, we learned how they were developed and evolved in response to real needs and challenges posed by the ever-changing landscape of that biotechnology. By analyzing how the post-2019 approach has engaged, or not engaged, the emerging biotechnology of xenotransplantation, we learned that there are important parallel needs and challenges posed by it, and likely most other emerging biotechnologies, that our post-2019 infrastructure cannot meet. While each emerging biotechnology is different, our national approach should involve:

1. A standing national committee adequately supported to conduct two functions:
   a. Scan the scientific horizon to ensure that we are able to prospectively plan for the emergence of significant biotechnologies, rather than playing catch-up after they come on the scene,
   b. Determine the process for establishing a specialized national committee devoted to an identified biotechnology on the horizon, populated with diverse and appropriate stakeholders (government and public, scientific and lay stakeholder, etc.). This mechanism would also develop principles to determine when this specialized committee, and accompanying database, are no longer necessary.[54]
2. When called for by 1.b., form a specialized national committee consisting of scientific experts and diverse stakeholders to engage with broad legal, social, and ethical issues of the biotechnology, as well as individual and public health risks, functions which include either advising or reviewing (whichever is appropriate at the time), educating and engaging with the public (including IRBs and IBCs), and reviewing and revising the national guidelines for public comment (see #4).
3. Flexible national guidelines that address the legal, social, and ethical issues of the biotechnology, boundaries of its acceptable use (at the time), and special considerations for both human subjects, close contacts, and the public, modeled on Appendix M/Points to Consider. Guidelines should be developed by the national body in consultation with as many sources

https://doi.org/10.1017/jme.2025.10210 Published online by Cambridge University Press

and resources as possible (ideally symposia or workshops, etc.). They should be published in the federal register for public comment, and the national body should respond to those comments. Guidelines should have endorsement from as many of the relevant federal agencies as possible to give them weight.

4. A national database of registered studies utilizing the biotechnology, with security measures but enough transparency to allow the review mechanisms (national body, IRBs, IBCs) to be able to compare adverse events and unintended consequences across different studies. This requirement could be satisfied by clinicaltrials.gov if it were enforced and contained adequate detail to make these assessments, or a specialized database that would come into existence and evolve alongside the reviewing body.

While it is clear that HGT research has advanced spectacularly over the last couple of decades, we must be careful not to assume that this technology has no more surprises in store. For example, while traditional somatic HGT for severe diseases appears to have reached the point in its trajectory where it no longer requires this special type of oversight, the questions of when, if ever, we should shift to doing somatic HGT for less severe conditions, in utero uses, and germline uses remains unclear. Gene Drive, CRISPR, and other applications of rDNA research also invite questions that are unresolved and require intentional collective engagement. This suggests that the RAC was not needed for the entire domain of HGT, and should perhaps have been altered to focus on review of emerging studies in these areas.

We also must approach new emerging technologies with the same level of thoughtfulness and care that were used to approach recombinant DNA technologies in their early years. There are ample pressures to pursue and expand novel biotechnologies, but we also know that the public support for these technologies can be quite precarious, and we need to approach them all with an eye to caution and protecting the public. The directors of the NIH and FDA are right that as biotechnologies evolve, we need to avoid impeding research with mechanisms that are redundant or unnecessary. Contrary to what the FDA and NIH directors would have us believe, the infrastructure put in place by the historical engagement with rDNA and HGT is not obsolete with the maturity of this biotechnology, but rather needs to be adapted as a framework so that it is ready to engage and address the analogous challenges posed by other emerging biotechnologies. These challenges require a national level, transparent conversation about what we think is ethical and safe to permit based on the current state of knowledge, and how we can implement these decisions in conversation with researchers and review bodies at the local level. With these mechanisms in place, emerging biotechnologies like xenotransplantation won't leap into the clinical space on a large scale before we have a reasonable process in place to guide them.

Acknowledgements. The author would like to acknowledge the support and experience provided by Garry Coulson, the Director and Institutional Biosafety Committee Chair at Clinical Biosafety Services, Sabai Global. His expertise on IBCs and their challenges motivated the initial question for this work, and his early consultation on the content was immensely helpful. The author is also appreciative of the staff and organization of Sabai IRB, as her experience working with them showed her the many challenges faced by IRBs and IBCs in their overlapping spaces.

Many thanks to Nada Gligorov, PhD, who completed the final revisions to this article after the untimely death of Stephanie Solomon Cargill.

Disclosures. The author has nothing to disclose.

Stephanie Solomon Cargill, PhD, MSPH, was Associate Professor of Bioethics at Alden March Bioethics Institute at Albany Medical College. She was also a member of the Board of Editors of *The Journal of Law, Medicine & Ethics*. She passed away during final revisions of this paper.

References

1. "Recombinant DNA Technology," National Human Genome Research Institute, https://www.genome.gov/genetics-glossary/Recombinant-DNA-Technology (last visited December 15, 2025).
2. There are a number of ways to define emerging technologies. The way in which this term is used throughout the paper is to designate either new technologies (e.g., xenotransplantation), or novel applications of established technologies (e.g., germline uses of rDNA) with uncertain risks and benefits in their application. Daniele Rotolo et al, "What is an emerging technology?" *Research Policy* 44, no.10 (2015): 1827–43, https://doi.org/10.1016/j.respol.2015.06.006.
3. The reason to opt for guidelines instead of regulations is because the latter are an inflexible mechanism not suitable for the ethical assessment of emerging technologies with uncertain risks and benefits. The three proposed mechanisms in this paper aim to provide guidance across different technologies, which might have significant differences in implementation and allocation. Regulations are mandatory and provide specific rules that would not have broad applicability across technologies such as xenotransplantation or germline editing, especially before we discover how those technologies should be regulated.
4. Donald S. Fredrickson, "Asilomar and Recombinant DNA: The End of the Beginning," in *Biomedical Politics*, ed. Kathi E. Hanna, (National Academies Press 1991): 258; Paul Berg et al, "Asilomar Conference on Recombinant DNA Molecules," *Science* 188, no. 4192 (1975): 991–94.
5. Donald S. Fredrickson, "The First Twenty-Five Years after Asilomar," *Perspectives in Biology and Medicine* 44, no. 2 (2001): 170–82, https://doi.org/10.1353/pbm.2001.0025.
6. This was technically the second Asilomar Conference, since the initial National Academy of Science meeting also took place at Asilomar.
7. Richard Hindmarsh and Herbert Gottweis, "Recombinant Regulation: The Asilomar Legacy 30 Years On." *Science as Culture* 14, no. 4 (2005): 299–307, https://doi.org/10.1080/09505430500368949.
8. See Fredrickson, "Asilomar and Recombinant DNA."
9. Stephen E. Toulmin, "Research and the Public Interest." *Research with Recombinant DNA: An Academy Forum* (National Academy of Sciences 1977), 101–106.
10. In stark contrast to the 1st generation RAC, this Director's Advisory Committee was populated with 20 members, which included scientists and medical experts that represented both the positions behind the Guidelines, such as attendees of Asilomar II, but also members who had been outspoken critics of this technology. It also included two college students, two ethicists, two lawyers, the President of the National Academic of Science, the president's consumer advocate, and a judge.
11. In the ensuing years, Congress attempted to pass regulations for recombinant DNA technology several times, without success.
12. Not coincidentally, this was shortly after the implementation of the National Research Act, which required institutional review boards to review all federally funded human subjects research.
13. Joseph M. Rainsbury, "Biotechnology on the RAC--FDA/NIH regulation of human gene therapy," *Food and Drug Law Journal* 55 (2000): 575.
14. President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, *Splicing Life: The Social and Ethical Issues of Genetic Engineering with Human Beings*, (United States National Technical Informational Service, 1982), 4.
15. Nelson A. Wivel and W. French Anderson, "Human Gene Therapy: Public Policy and Regulatory Issues," in *The Development of Human Gene Therapy*, ed. Theodore Friedman, (Cold Spring Harbor Laboratory Press, 1999), 671–89
16. United States Congress Office of Technology Assessment, "Human Gene Therapy — Background Paper" (Government Printing Office, 1984),

https://doi.org/10.1017/jme.2025.10210 Published online by Cambridge University Press

https://repository.library.georgetown.edu/handle/10822/548858 (last visited December 15, 2025). There is notably *not* a consensus about germline gene therapy or use of somatic gene therapy for enhancement.
17. "Points to Consider in Human Somatic Cell Therapy and Gene Therapy" *Human Gene Therapy* 2, no. 3 (1991): 251–56, https://doi.org/10.1089/hum.1991.2.3-251
18. "About NIH, Mission and Goals," National Institutes of Health, https://www.nih.gov/about-nih/mission-goals (last visited December 15, 2025).
19. "What We Do, FDA Mission" United States Food and Drug Administration, https://www.fda.gov/about-fda/what-we-do (last visited December 15, 2025).
20. Aaron P. Mitchell et al, "The Prescription Drug User Fee Act: Much More Than User Fees," *Medical Care* 60, no. 4 (2022): 287–93, https://doi.org/10.1097/mlr.0000000000001692.
21. See Rainsbury, "Biotechnology on the RAC--FDA/NIH regulation of human gene therapy."
22. The document mentions risks to close contacts in one sentence near the end: "Use of viral vectors may in special cases require testing of clinical personnel or household contacts to confirm lack of infectious spread."
23. "Historical Highlights of ClinicalTrials.Gov," Boston University Medical Campus and Boston Medical Center, https://www.bumc.bu.edu/irb/files/2019/11/Historical-Highlights-of-ClinicalTrials.pdf (last visited December 15, 2025).
24. Although Gelsinger had the deficiency, he had a mild form that was relatively well-controlled with existing therapies.
25. Institute of Medicine, *Oversight and Review of Clinical Gene Transfer Protocols: Assessing the Role of the Recombinant DNA Advisory Committee* (National Academies Press, 2014), https://doi.org/10.17226/18577. [hereinafter cited as 2014 Report]; See Rainsbury, "Biotechnology on the RAC--FDA/NIH regulation of human gene therapy."
26. See 2014 Report.
27. Daniel Eisenman and Scott Swindle, "FDA Guidance on Shedding and Environmental Impact in Clinical Trials Involving Gene Therapy Products," *Applied Biosafety* 27, no. 3 (2022): 191–97, https://doi.org/10.1089/apb.2022.0020; Daniel Eisenman, "The United States' Regulatory Environment Is Evolving to Accommodate a Coming Boom in Gene Therapy Research," *Applied Biosafety* 24, no. 3 (2019): 147–52, https://www.liebertpub.com/doi/pdf/10.1177/1535676019854866 (last visited December 15, 2025).
28. 45 C.F.R.§ 46.111.a2 (2017).
29. Nelson A. Wivel, "Historical Perspectives Pertaining to the NIH Recombinant DNA Advisory Committee," *Human Gene Therapy* 25, no. 1 (2014): 19–24, https://doi.org/10.1089/hum.2013.2524; 2014 Report.
30. Frances S. Collins and Scott Gottlieb, "The Next Phase of Human Gene-Therapy Oversight," *New England Journal of Medicine* 379, no. 15 (2018): 1393–95, https://doi.org/10.1056/NEJMp1810628.
31. James M. Wilson, "The RAC Retires After a Job Well Done," *Human Gene Therapy Clinical Development* 29, no. 3 (2018): 115–117, https://doi.org/10.1089/humc.2018.29034.wil; Xandra O. Breakefield, "Refocus the Recombinant DNA Advisory Committee," *Nature Medicine* 18, no. 7 (2012): 1007, https://doi.org/10.1038/nm0712-1007. Notably, the authors of these two publications are James Wilson, the gene therapy pioneer and also PI on the trial where Jesse Gelsinger passed away; and the president of the American Society of Gene and Cell Therapy, respectively.
32. See Collins and Gottlieb, "The Next Phase of Human Gene-Therapy Oversight."
33. David K.C. Cooper et al, "A Brief History of Clinical Xenotransplantation," *International Journal of Surgery* 23 (2015): 205–10, https://doi.org/10.1016/j.ijsu.2015.06.060.
34. Institute of Medicine, *Xenotransplantation: Science, Ethics, and Public Policy* (National Academies Press, 1996), https://doi.org/10.17226/5365 [hereinafter cited as IOM Report]
35. "History & Mission," International Xenotransplantation Association, https://tts.org/ixa-about/ixa-history-mission (last visited December 15, 2025).
36. Center for Biologics Evaluation and Research, *PHS Guideline on Infectious Disease Issues in Xenotransplantation* (U.S. Food and Drug Administration, 2001), 2–3, https://www.fda.gov/regulatory-information/search-fda-guidance-documents/phs-guideline-infectious-disease-issues-xenotransplantation (last visited December 15, 2025) [hereinafter cited as PHS Guideline]
37. See PHS Guideline, 42-43.
38. Secretary's Advisory Committee on Xenotransplantation, *Informed Consent in Clinical Research Involving Xenotransplantation: Draft* (U.S. Department of Health and Human Services, 2004), https://www.tts.org/77-ixa/ixa-news/434-ixa-islet-recommendations (last visited December 15, 2025).
39. "Breaking Ground in Transplantation: A New Era in Xenotransplantation," National Kidney Foundation, May 31, 2024, https://www.kidney.org/news-stories/breaking-ground-transplantation-new-era-xenotransplantation (last visited December 15, 2025.
40. "Novel and Exceptional Technology and Research Advisory Committee (NExTRAC)," National Institutes of Health Office of Science Policy, https://osp.od.nih.gov/policies/novel-and-exceptional-technology-and-research-advisory-committee-nextrac/ (last visited December 15, 2025) [hereinafter cited as NExTRAC Website]
41. Novel and Exceptional Technology and Research Advisory Committee (NExTRAC) Working Group, "Report to Establish a NExTRAC Framework," (National Institutes of Health Office of Science Policy, December, 2020) [hereinafter cited as NExTRAC Report], https://osp.od.nih.gov/wp-content/uploads/NExTRAC-Framework-Report_FINAL_508.pdf (last visited December 15, 2025).
42. See NExTRAC Report, 8.
43. Daniel J. Hurst et al, "Recommendations to the IRB review process in preparation of xenotransplantation clinical trials," *Xenotransplantation* 27, no. 2 (2020): 1–9, https://doi.org/10.1111/xen.12587 [hereinafter Hurst et al (2020)]; Daniel J. Hurst et al, "Close contacts of xenograft recipients: Ethical considerations due to risk of xenozoonosis," *Xenotransplantation* 31, no. 2 (2024): e12847 [hereinafter Hurst et al (2024)], https://doi.org/10.1111/xen.12847; Fritz H. Bach et al, "Uncertainty in xenotransplantation: Individual benefit versus collective risk," *Nature Medicine* 4 (1998): 141–44, https://doi.org/10.1038/nm0298-141.
44. See NExTRAC Website.
45. Lawrence A. Tabak, "CHARGE TO NExTRAC, ENGAGING THE PUBLIC AS PARTNERS IN CLINICAL RESEARCH" in *NIH NexTRAC, August 29, 2023 Meeting Minutes* (U.S. Department of Health and Human Services, 2023), https://osp.od.nih.gov/events/novel-and-exceptional-technology-and-research-advisory-committee-4 (last visited December 15, 2025).
46. See Hurst et al (2020), Hurst et al (2024).
47. Jeffrey P. Kahn and Anna C. Mastroianni, "Sunset on the RAC: When Is It Time to End Special Oversight of an Emerging Biotechnology?," *American Journal of Bioethics* 18, no. 12 (2018): 1–2, https://doi.org/10.1080/15265161.2018.1540650.
48. See 2014 Report.
49. See IOM Report, 2.
50. See MMWR Recommendations and Reports, "U.S. Public Health Service Guideline on Infectious Disease Issues in Xenotransplantation," Centers for Disease Control, August 24, 2021, https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5015a1.htm.
51. See Collins and Gottlieb, "The Next Phase of Human Gene-Therapy Oversight."
52. This topic of confidentiality with emerging technologies is challenging and crucial. They need transparency so that the adverse events and unintentional consequences from different trials can be shared to ensure review, but they also need to acknowledge the risks of public exposure of proprietary information. This issue is outside the scope of this paper, but definitely needs careful thought.
53. See Hurst et al (2020), Hurst et al (2024).
54. Kahn and Mastroianni, "Sunset on the RAC."

https://doi.org/10.1017/jme.2025.10210 Published online by Cambridge University Press