DISCUSSION PAPER

Regenerative Medicine

Case Study for Understanding and Anticipating Emerging Science and Technology

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This discussion paper is one in a series of three that present case studies of emerging science and technology applications in order to better understand, anticipate, and develop governance for similar emerging technologies, with attention to their potential societal, ethical, legal, and health-related impacts. These case studies were developed by members, academic collaborators, and staff of the National Academy of Medicine's Committee on Emerging Science, Technology, and Innovation in Health and Medicine (CESTI) and should be used to spur conversation and further investigation into the potential impacts of emerging technologies. Read more about CESTI at https://nam.edu/programs/committee-on-emerging-science-technology-and-innovation-in-health-and-medicine.

Introduction

This case study was developed as one of a set of three studies, focusing on somewhat mature but rapidly evolving technologies. These case studies are intended to draw out lessons for the development of a cross-sectoral governance framework for emerging technologies in health and medicine. The focus of the case studies is the governance ecosystem in the United States, though where appropriate, the international landscape is included to provide context. Each of these case studies:

- describes how governance of the technology has developed within and across sectors and how it has succeeded, created challenges, or fallen down;
- outlines ethical, legal, and social issues that arise within and across sectors;
- considers a multitude of factors (market incentives, intellectual property, etc.) that shape the evolution of emerging technologies; and
- identifies key stakeholders.

Each case study begins with two short vignettes designed to highlight and make concrete a subset of the ethical issues raised by the case (see *Box 1* and *Box 2*). These vignettes are not intended to be comprehensive but rather to provide a sense of the kinds of ethical issues being raised today by the technology in question.

BOX 1 | Regenerative Medicine Vignette 1

In 2023, Amber is considering her options. She has spent much of her life struggling to access high-quality care for her sickle cell disease. Inadequate care and pain management prolong her hospital stays, extending her time away from both her young family and her demanding job at a local financial services firm. She recently learned of a new clinical trial involving a genetically modified autologous (meaning her own cells) stem cell transplant, which is recruiting in a neighboring state. While risky and time-consuming in its own right, the trial offers a potential cure for her disease, which would not only improve quality of life for her and her family but could also be an end run around her struggles with accessing care for her chronic disease. Amber believes she could live a full life with well-controlled disease, but as that has not been her experience to date, the clinical trial feels like her and her family's best chance for a healthy future.

Potential benefits: Potential cure, potentially decades of symptom relief and health

Potential concerns: Serious risks of morbidity and mortality associated with the clinical trial, long in-patient stay, impact of inadequate chronic and acute disease care on risk/benefit analysis

BOX 2 | Regenerative Medicine Vignette 2

In 2022, Youssef has been living with thalassemia his whole life. Now 22 and out of college, he is both eager and anxious about undergoing allogeneic stem cell transplantation. His thalassemia has been managed for most of his life through chronic blood transfusion and iron chelation, which, while reasonably effective, come with side effects and serious long-term complications including organ damage from iron buildup, and they are time-consuming and expensive. While a transplant comes with serious risks, he knows that it is much safer than it used to be and could lead to complete remission of his disease. He and his doctors have decided that the time has come to attempt a transplant, but he has not been able to find a well-matched donor thus far. Youssef is an only child, his extended family lives in Egypt, and he has not been able to find an unrelated donor through the various donor registries due to his relatively unique human leukocyte antigen (HLA) haplotype and the low representation of non-European diversity in the registries. He has begun to consider using a less-than-perfect donor for his transplant, which would increase the risks but would still give him a chance at a cure. In recent years, the treatments for graft-versus-host disease have improved, making a less-than-perfect donor a more viable option.

Potential benefits: Potential cure, potential extension of lifespan

Potential concerns: Lack of diverse donor population, risks of less-than-perfectly matched transplant, cost of both standard of care and curative transplant

The cases are structured by a set of guiding questions, outlined subsequently. These questions are followed by the historical context for the case to allow for clearer understanding of the trajectory and impact of the technology over time and the current status (status quo) of the technology. The bulk of the case consists of a cross-sectoral analysis organized according to the following sectors: academia, health care/nonprofit, government, private sector, and volunteer/consumer. Of note, no system of dividing up the world will be perfect—there will inevitably be overlap and imperfect fits. For example, "government" could be broken into many categories, including international, national, tribal, sovereign, regional, state, city, civilian, or military. The sectoral analysis is further organized into the following domains: science and technology, governance and enforcement, affordability and reimbursement, private companies, and social and ethical considerations. Following the cross-sectoral analysis is a broad, nonsectoral list of additional questions regarding the ethical and societal implications raised by the technology.

The next section of the case is designed to broaden the lens beyond the history and current status of the technology at the center of the case. The "Beyond" section highlights additional technologies in the broad area the focal technology occupies (e.g., neurotechnology), as well as facilitating technologies that can expand the capacity or reach of the focal technology. The "Visioning" section is designed to stretch the imagination to envision the future development of the technology (and society), highlighting potential hopes and fears for one possible evolutionary trajectory that a governance framework should take into account.

Finally, lessons learned from the case are identified—including both the core case and the visioning exercise. These lessons will be used, along with the cases themselves, to help inform the de-

velopment of a cross-sectoral governance framework, intended to be shaped and guided by a set of overarching principles. This governance framework will be created by a committee of the National Academies of Sciences, Engineering, and Medicine (https://www.nationalacademies.org/our-work/creating-a-framework-for-emerging-science-technology-and-innovation-in-health-and-medicine).

Case Study: Regenerative Medicine

Regenerative medicine as a field is quite broad but is generally understood to focus on the regeneration, repair, and replacement of cells, tissues, and organs to restore function (Mason and Dunnill, 2008). The aspect of regenerative medicine on which this case study focuses relates to the ability to treat—or cure—genetic hematologic disease safely and effectively, and the significant trade-offs that come with these novel therapies.

The story of this therapy begins in the history of bone marrow transplants. The medicinal value of bone marrow has long been recognized and was first discussed in the 1890s as a potential treatment (administered orally) of "diseases believed to be characterized by defective hemogenesis" (Quine, 1896).

While allogeneic bone marrow transplant (in which stem cells from a donor are collected and transplanted into the recipient) may be the most broadly known form of hematopoietic stem and progenitor cell (HSPC) transplant, a range of other cell types are also used. HSPCs used in transplant can be either allogeneic (i.e., from a donor) or autologous (i.e., from the person who will also receive the transplant). The cells used in transplant research and clinical care can come from bone marrow, peripheral blood stem cells (PBSCs), umbilical cord blood, and pluripotent stem cell–derived cells.

A major challenge throughout the history of HSPC transplantation has been the dire risks associated with these transplants, including the morbidity and mortality caused by immunological reactions between the transplanted cells and the tissues of the recipient. In particular, graft-versus-host disease (GVHD) is a serious response in which the transplanted stem cells view the recipient's tissues as foreign and mount an immune response, attacking the recipient's body. If an autologous transplant is not possible given the nature of the disease to be treated, an immunologically well-matched healthy donor for allogeneic transplant is critical. For genetic hematologic disease, a new approach that would not only treat but cure the condition is now being tested: genetic modification of the patient's own HSPCs to correct or compensate for the defect, followed by transplantation of the corrected autologous cells.

This challenge of matching transplantable cells to patients has driven evolution within the field of regenerative medicine, including logistical fixes in the form of HSPC registries and banks to technological approaches including the use of pluripotent stem cell–derived cell sources and genome editing (e.g., clustered regularly interspaced short palindromic repeats [CRISPR]).

This challenge of immunological matching has also driven significant ethical challenges, even beyond the substantial risks of HSPC transplantation itself. In contrast to many novel technologies, where finances are a primary barrier to access, in the case of regenerative medicine, there is the additional barrier of biology. People who are not of European descent have a lower probability of finding well-matched donors than do people of European descent. Furthermore, genetic hematologic diseases like sickle cell disease (SCD) and thalassemia, for which HSPC transplant is the only established cure (and a fraught one, at that), have struggled to garner the financial and grant support needed to move research forward. This challenge persists despite SCD being three times more prevalent in the United States than cystic fibrosis, which has historically benefited from generous public and private funding (Farooq et al., 2020; Wailoo and Pemberton, 2006). All of this stands on a background of long-understood barriers even to standard of care (e.g., adequate pain management) for individuals with SCD in particular (Haywood et al., 2009). Together, these facts raise concerns related to equity and access at multiple stages of research, development, and clinical care.

Finally, advances in this science have also attracted the attention of those who are willing to take advantage of patients under the guise of cutting-edge therapy, creating a robust market of direct-to-consumer (DTC) cell-based services and interventions that at best waste time and money and at worst cause serious harm or death (Bauer et al., 2018).

Guiding Questions (derived from Global Neuroethics Summit Delegates, 2018; Mathews, 2017)

The following guiding questions were used to frame and develop this case study.

- **Historical context:** What are the key scientific antecedents and ethics touchstones?
- **Status quo:** What are the key questions, research areas, and products/applications today?
- **Cross-sectoral footprint:** Which individuals, groups, and institutions have an interest or role in emerging biomedical technology?
- **Ethical and societal implications:** What is morally at stake? What are the sources of ethical controversy? Does this technology or application raise different and unique equity concerns?

Additional guiding questions to consider include the following:

- **Key assumptions around technology:** What are the key assumptions of both the scientists around the technology and the other stakeholders that may impede communication and understanding or illuminate attitudes?

- **International context and relevant international comparisons:** How are the technology and associated ethics and governance landscape evolving internationally?
- **Legal and regulatory landscape:** What are the laws and policies that currently apply, and what are the holes or challenges in current oversight?
- **Social goals of the research:** What are the goals that are oriented toward improving the human condition? Are there other goals?

Historical Context

What are the key scientific antecedents and ethics touchstones?

HSPC Transplant

HSPC transplant was initially only attempted in terminally ill patients (Thomas, 1999). The first recorded bone marrow transfusion was given to a 19-year-old woman with aplastic anemia in 1939 (Osgood et al., 1939). This was long before the Nuremburg Code, the Declaration of Helsinki, or the Belmont Report and anything like current understandings of informed consent (NCPHSBBR, 1979; Rickham, 1964; International Military Tribunal, 1949). There was also little understanding of the factors associated with graft failure—no attempts at bone marrow transfusions succeeded, and all patients died. Despite this early experience, the consequences of World War II, particularly the need to improve radiation and burn injury treatment, propelled this work forward (de la Morena and Gatti, 2010).

As human transplant work continued, experiments in mice and dogs in the 1950s and 1960s showed that after lethal radiation, these animals would recover if given autologous bone marrow. However, if given allogeneic marrow, the animal would reject the graft and die or accept the graft but then die from "wasting syndrome," which later came to be understood as GVHD (Mannick et al., 1960; Billingham and Brent, 1959; Barnes et al., 1956; Rekers et al., 1950). It became clear that close immunologic matching between donor and recipient and management of GVHD in the recipient would be vital to the success of allogeneic bone marrow transplants (de la Morena and Gatti, 2010).

A 1970 accounting of the reported experience with HSPC transplants to date described approximately 200 allogeneic stem cell graft attempts (six involving fetal tissue) in subjects aged less than 1 to over 80 years, most of which had taken place between 1959 and 1962 (Bortin, 1970). (Of note, there were likely scores of unreported cases; in fact, the author ended the article with a call for reporting of all HSPC transplant attempts to the newly established American College of Surgeons-National Institutes of Health Organ Transplant Registry.) Of the reported cases (which often included the subjects' initials), only 11 individuals were "unequivocal" allogeneic chimeras, and of those, only five were still alive at the time their case was reported. Many of the reported subjects died of opportunistic infections or GVHD, the noting of which often did not capture the true human toll of these deaths. For many years, even "success" (i.e., engraftment of the transplanted marrow) ended in death due to these other causes (Mathé et al., 1965; Thomas et al., 1959). As Donnall Thomas, a pioneer and leader in the field who won the Nobel Prize for "discoveries concerning organ and cell transplantation in the treatment of human disease" in 1990, reflected years later, "the experience with allogeneic transplants had been so dismal that questions were raised about whether or not such studies should be continued" (Thomas, 2005; Nobel Prize, 1990). In fact, the dismal experience with HSPC transplant eventually led most investigators to discontinue this work in humans, the focus returning for a time to animal studies (Little and Storb, 2002).

However, the discovery of human leukocyte antigen (HLA) in 1958 by Jean Dausset, which helps the immune system differentiate between what is "self" and what is foreign, and subsequent advances in the understanding of HLA matching and immunosuppression during the 1960s and 1970s led to a resumption of human clinical trials (Nobel Prize, 1980). In 1971, the first successful use of HSPC transplant to treat leukemia was reported (Granot and Storb, 2020). The following decades saw additional developments in HSPC transplant, improving the safety of the intervention, thus enabling its consideration for treatment of a broader array of blood diseases, including the hemoglobinopathies (Granot and Storb, 2020; Apperley, 1993).

The first use of HSPC transplant to cure thalassemia was in 1981, in a 16-month-old child, with an HLA-identical sibling donor—this patient was alive and thalassemia-free more than 20 years later (Bhatia and Walters, 2008; Thomas et al., 1982). Thalassemia major (the most serious form of the disease) requires chronic blood transfusion and chelation for life, a process which leads to gradual iron buildup and related organ damage, including heart failure, which is a common cause of death. Life expectancy for treated patients has increased substantially and varies by thalassemia type and treatment compliance, but patients can now live into their 40s and beyond (Pinto et al., 2019).

The first cure of SCD via HSPC transplant was incidental. An 8-year-old girl with acute myeloid leukemia (AML) was successfully treated for her leukemia with a bone marrow transplant, curing her SCD in the process (Johnson et al., 1984). By this time, life expectancy for an individual with SCD had improved substantially, reaching the mid-20s due to advances in understanding and treatment of the disease (particularly the use of antibiotics to manage the frequent infections that plagued those with the disease) (Wailoo, 2017; Prabhakar et al., 2010). The first five patients, all children, in whom HSPC transplants were used intentionally to treat SCD were reported in 1988 (Vermylen et al., 1988). As Vermylen and colleagues reported, "In all cases there was complete cessation of vaso-occlusive episodes and haemolysis" (Vermylen et al., 1988).

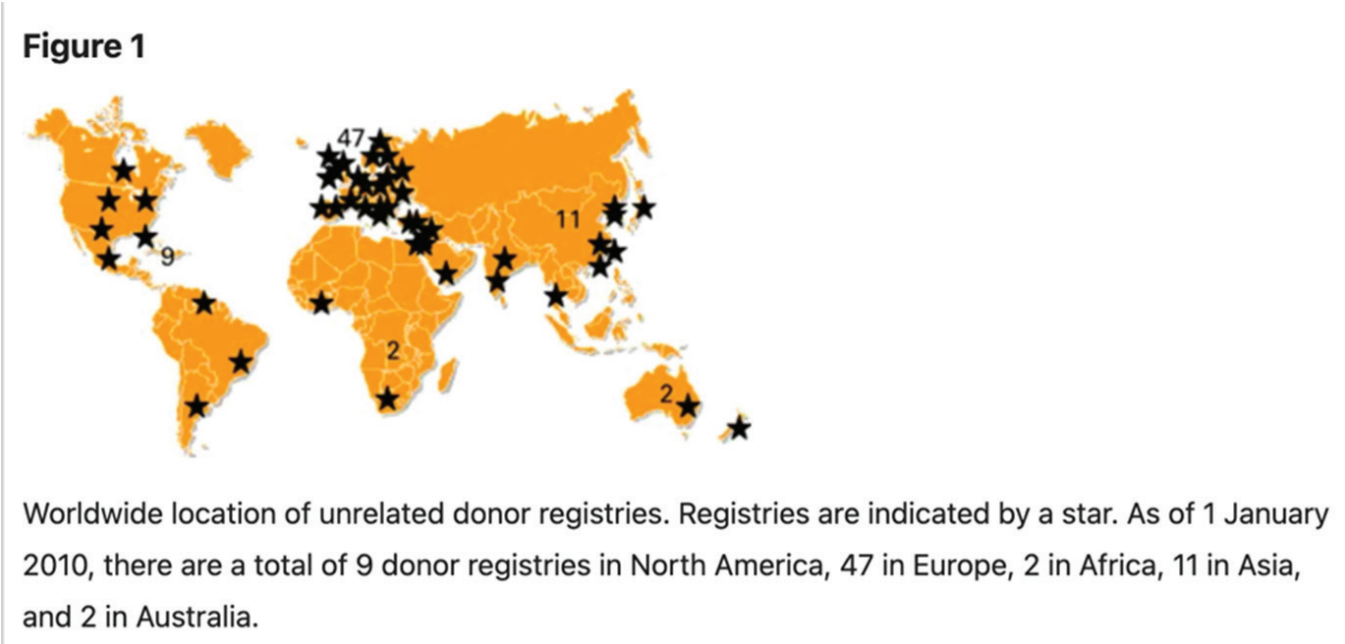
Around this same time, there were also advancements in the sources of transplantable hematopoietic cells, expanding beyond bone marrow to include peripheral blood stem cells and umbilical cord blood (Gluckman et al., 1989; Kessinger et al., 1988). Cord blood was particularly appealing for a number of reasons, including that it is less immunogenic than the other cell sources, reducing the risk of GVHD.

The development of cord blood transplant has a very different origin story to that of bone marrow, beginning with a hypothesis and the founding of a company (Ballen et al., 2013). The company, Biocyte Corporation (later PharmaStem Therapeutics), funded the early work and held two short-lived patents over the isolation, preservation, and culture of umbilical cord blood (Shyntum and Kalkreuter, 2009). The longevity of the science has thankfully surpassed that of the company that launched it. The first cord blood–based HSPC transplant was conducted with the approval of the relevant institutional review boards (IRBs) and the French National Ethics Committee, to treat a 5-year-old boy with Fanconi anemia using cells from the birth of an unaffected, HLA-matched sister (Ballen et al., 2013; Gluckman et al., 1989). The success of the early cases (the 5-year-old boy was still alive and well 25 years later) led to the use of unrelated cord blood transplant and expansion of use beyond malignant disease (Ballen et al., 2013; Kurtzberg et al., 1996). Benefits of cord blood include noninvasive collection, ability to cryopreserve characterized tissue for ready use, reduced likelihood of transmitting infections, and lower immunogenicity relative to bone marrow, enabling imperfect HLA matching and expanding access, in particular for people not of European descent (Barker et al., 2010; Gluckman et al., 1997). Cord blood HSPC transplant was first used primarily in children, because it was thought that the relatively low number of cells in a cord blood unit would limit its use in adults, but over time, as techniques and supportive care have improved, so has success of cord blood transplant in adults (Eapen et al., 2010; Ballen et al., 2007). Today, cord blood is widely used for HSPC transplants in both children and adults, with outcomes as good as or better than with bone marrow. Despite these advancements, however, allogeneic HSPC transplant continued to depend on the availability of HLA-matched donors.

Public HSPC Banks

Unfortunately, only about 35 percent of patients have HLA-matched siblings, so patients have needed to look beyond their immediate family for matched donors. This need led to the creation of HLA-typed donor registries, starting with the founding of the Europdonor registry in the Netherlands in 1970 and the International Blood and Marrow Transplant Registry at the Medical College of Wisconsin in 1972 (McCann and Gale, 2018). In 1986, the National Marrow Donor Program (NMDP), which operates the Be the Match registry, was founded by the U.S. Navy. Other registries in the United States and Europe followed, and by 1988, there were eight active registries around the world with more than 150,000 donors (van Rood and Oudshoorn, 2008). The Bone Marrow Donors Worldwide network, which connected these registries, was formed in 1988 to facilitate the identification of potential donors, and in 2017 its activities were taken over by the World Marrow Donor Association (WMDA) (Oudshoorn

FIGURE 1 | Worldwide Location of Unrelated Donor Registries



SOURCE: Ballen, K. K., E. Gluckman, and H. E. Broxmeyer. 2013. Umbilical cord blood transplantation: The first 25 years and beyond. *Blood* 122(4):491–498. https://doi.org/10.1182/blood-2013-02-453175.

et al., 1994). Today, the combined registry includes more than 37,600,000 donors and more than 800,000 cord blood units from 54 different countries (see *Figure 1*) (WMDA, 2021; Petersdorf, 2010).

However, even with tremendous global collaboration to identify and make available donor information, access is not equal. The NMDP estimates suggest that while approximately 90 percent of people of European descent will identify a well-matched unrelated marrow donor, the same will be true for only about 70 percent of people of Asian or Hispanic descent and 60 percent of those of African descent (Pidala et al., 2013). Causes for this disparity include higher HLA diversity among these populations compared to those of European descent and smaller numbers of racial and ethnic minority volunteers in donor registries and ultimately available for transplant (Sacchi et al., 2008; Kollman et al., 2004).

Private HSPC Banks

Alongside the public registries, trading on the success of cord blood HSPC transplants and playing on the fears of new parents, a thriving market of private cord blood banks has developed (Murdoch et al., 2020). These for-profit private banks market their services—collecting and storing cord blood for potential future personal use—as insurance policies for the health of one's newborn, without much data to support the claim. While donation of cord blood to a public bank is free to the donor, costs associated with private banking include a collection fee (US$1,350–$2,300) and annual storage fees ($100–$175/year), which are unlikely to be covered by health insurance (Shearer et al., 2017). At the same time, public banks are held to transparent, rigorous storage and quality standards that do not apply to private banks, leading to lower overall quality of cord blood in private banks (Shearer et al., 2017; Sun et al., 2010; Committee on Obstetric Practice, 2008). Finally, cord blood stored in public banks is 30 times more likely to be accessed for clinical use than samples stored in private banks, and there is broad professional consensus, and associated professional guidance, that public banking is preferable to private banking (Shearer et al., 2017; Ballen et al., 2015). Despite these differences, in 2017, there were about 800,000 cord blood units in public banks, compared with more than 5 million in private banks (Kurtzberg, 2017).

New HSPC Sources

While adult stem cell sources (bone marrow, peripheral blood, and cord blood) have dominated research and clinical care for many decades, in the late 1990s and mid-2000s, new tools were added in the form of several pluripotent stem cell types, including embryonic stem cells, embryonic germ cells, nuclear transfer (NT)-derived stem cells, and most recently, induced pluripotent stem cells (iPSCs) (Tachibana et al., 2013; Yu et al., 2007; Takahashi and Yamanaka, 2006; Shamblott et al., 1998; Thomson et al., 1998). In contrast to the previous cell sources, which are restricted to repopulating blood cell types, these new pluripotent stem cells can turn into any of the approximately 220 cell types in the human body and have a correspondingly diverse array of potential applications. For the purposes of this case, the authors focus on the use of these cells in hematologic disease, but understanding some of the history of the development and use of these cells is helpful for the broader goals of the case. Importantly, these new cell types emerged in a very different regulatory and societal environment than the environment in which bone marrow transplants were first being developed.

The first derivations of human embryonic stem cells (ESCs) and embryonic germ cells (EGCs) were published in 1998 (Shamblott et al., 1998; Thomson et al., 1998). Both of these seminal papers concluded with discussion of the potential for the use of these cells in transplantation-based treatments and cures and emphasized the need to address the challenge of immune rejection, either through the development of cell banks, akin to the registries described previously, or through the genetic modification of the cells to create universal donor cells or to match the particular cellular therapy to the particular patient.

Unlike bone marrow or cord blood, however, the source of these cells was human embryos and fetal tissue, and at the time of these publications, there was already a notable history of governance of these tissues (Matthews and Yang, 2019; Green, 1995; NIH, 1994). In addition, the Dickey-Wicker Amendment had been in place for 3 years, prohibiting the use of federal funds to create human embryos for research or to conduct research in which human embryos are "destroyed, discarded, or knowingly subjected to risk of injury or death" (104th Congress, 1995). Within weeks of the papers' publication, a legal opinion was issued from the Department of Health and Human Services (HHS) interpreting Dickey-Wicker with regard to the new research (Rabb, 1995). Though federal dollars could not be used to create ESCs or EGCs, it was determined that federal dollars could be used to conduct research with pluripotent stem cells thus derived. This interpretation was supported later that year by a report of the National Bioethics Advisory Commission (NBCA, 1999). This did not, however, settle the issue.

A year later, President George W. Bush was elected following a campaign in which he made clear his opposition to this research (Cimons, 2001). In August 2001, in his first address to the nation, President Bush announced that federal funding would be permitted for research using the approximately 60 ESC lines already in existence at the time of his announcement, but not for research with newly derived lines (CNN, 2001). The president seemed to be attempting to walk a fine line between allowing promising research to move forward and not causing the federal government (and taxpayers) to be complicit in the destruction of human embryos. Ultimately, many of these 60 approved "Bush lines" proved impossible to access or difficult to work with. Furthermore, the accounting required in institutions and laboratories

working with both "Bush lines" and newer lines was daunting (Murugan, 2009).

As ethical and policy debates raged, states began passing their own legislation governing human ESC research, beginning with California, and creating over time a patchwork of state-level policy that ranged from providing government funding for ESC research, as in California, to classifying the work as a felony, such as in Arizona (CIRM.ca.gov, n.d.; Justia US Law, 2020). In 2005, Congress passed its own bill that would permit federal funding of research with an expanded number of human ESC lines, but the bill was subsequently vetoed by President Bush (109th Congress, 2005). The same year, the National Research Council and the Institute of Medicine published its tremendously influential report titled *Guidelines for Human Embryonic Stem Cell Research* (IOM and NRC, 2005). These guidelines led to highly effective self-regulation in the field, as the *Guidelines* were adopted across the United States at institutions conducting human ESC research (Robertson, 2010). The *Guidelines* recommended the creation of a new institutional oversight committee to review ESC research, similar to IRBs, among other recommendations. The *Guidelines* remained the primary source of governance for ESC research through the end of the Bush administration.

An additional scientific innovation during this time was the announcement of the creation of iPSCs in 2006 (Nobel Prize, 2012; Takahashi and Yamanaka, 2006). iPSCs are derived from somatic tissue, not embryonic or fetal tissue, through the introduction of a small set of transcription factors that effectively reset the mature cell back to a pluripotent state. This concept had actually been introduced as an alternative to ESCs by President Bush's bioethics commission, though it had been met with skepticism, and Shinya Yamanaka's announcement at the 2006 International Society for Stem Cell Research (ISSCR) annual meeting stunned the assembled scientists (Scudellari, 2016; The President's Council on Bioethics, 2005). This scientific end-run around the destruction of human embryos led to a flood of new researchers, as scientists now needed only somatic cells, rather than highly regulated embryonic or fetal tissue, to participate in this new wave of regenerative medicine research.

By the end of President Bush's second term, in addition to the National Academies' *Guidelines*, guidelines were also issued from the ISSCR and a number of other academic groups (ISSCR, n.d.; The Hinxton Group, 2006). Internationally, as in the United States, a patchwork of policy responses had emerged, ranging from very restrictive to permissive to supportive, leading both domestically and internationally to a degree of "brain drain" as some scientists relocated to jurisdictions that permitted this research (Verginer and Riccaboni, 2021; Levine, 2012).

When President Barack Obama took office in 2009, he issued an Executive Order reversing former president Bush's prior actions (White House, 2009). Rather than establishing the final rules himself, he permitted funding of ESC research "to the extent permitted by law" (a nod to the Dickey-Wicker Amendment) and charged the National Institutes of Health (NIH) with developing guidelines for such funding. The NIH guidelines, which largely followed the *Guidelines*, were finalized in July 2009 and were promptly tied up in a years-long battle in the courts until the Supreme Court declined to hear the final appeal in 2013, leaving the NIH guidelines intact (NIH, 2013, 2009).

Genetic Modification

The final piece of the regenerative medicine puzzle is the need to overcome immune rejection of transplanted cells. As noted in the initial HPSC papers, potential ways to overcome immune rejection (in the absence of iPSCs) included both banking of a large number of diverse cell lines and genetic modification of the cells intended for transplant, although at the time the technology to do so did not exist (Faden et al., 2003). Gene therapy of this sort had been contemplated for years, and gene transfer trials had begun in the 1990s using the tools scientists had at the time (IOM, 2014). Governance structures grew up around these trials, including the transition of the Recombinant DNA Advisory Committee (RAC) from reviewing NIH-funded research involving recombinant DNA (rDNA) to reviewing gene transfer protocols (IOM, 2014). Of note, though the RAC served as a model internationally for the governance of rDNA research, its mandate was repeatedly questioned and its work critiqued, even as its role evolved (IOM, 2014). As the pace and volume of gene transfer research picked up, the pace of review slowed. Responding not only to the resulting critiques but also the accumulated experience and data, the RAC relaxed restrictions and expedited reviews where possible, ultimately pivoting again to a focus on novel protocols, and leaving more straightforward protocols to the U.S. Food and Drug Administration (FDA) to approve or deny (IOM, 2014). But the original vision of genetically tailored cellular therapy articulated in the 1998 papers did not become possible until almost 15 years later.

In 2012, the publication of the paper that introduced clustered regularly interspaced short palindromic repeats-CRISPR associated protein 9 (CRISPR-Cas9) launched a new era of genetic modification (Jinek et al., 2012). This new tool dramatically improved upon prior gene editing tools with respect to technical ease, speed, and cost, putting the kind of editing imagined in the 1998 papers within reach.

Status Quo

What are the key questions, research areas, and products or applications today?

HSPC Transplant Access

Today, median health care costs for HSPC (including the procedure and 3 months of follow-up) in the United States are approximately $140,000–$290,000, depending on the type of procedure (Broder et al., 2017). While 200-day nonremission mortality has decreased substantially since 2000, it remains

high (11%) (McDonald et al., 2020). The risks of transplant remain a significant barrier to access, in particular for those with nonmalignant disease, such as SCD. Beyond this, and as noted previously, there are significant ethnic and racial disparities in access to HSPC transplant, largely due to the relatively lower probability of identifying a well-matched HSPC donor (Barker et al., 2019). A recent study demonstrated that while White patients of European descent have a 75 percent chance of finding a well-matched (8/8 HLA-matched) donor, for White Americans of Middle Eastern or North African descent, the probability is 46 percent (Gragert et al., 2014). For Hispanic, Asian, Pacific Islander, and Native American individuals, the probability of such a match ranges from 27 to 52 percent, and for Black Americans, the probability is 16–19 percent (Gragert et al., 2014). Contributing to these disparities for racial and ethnic minority groups are higher HLA diversity, smaller numbers of racial and ethnic minority volunteers in donor registries, and the higher rates at which matched minority volunteers become unavailable for donation (e.g., due to inability to reach the volunteer or medical deferral due to diabetes, asthma, infectious disease, or other identified condition) (Sacchi et al., 2008; Kollman et al., 2004). Giving preference to 8/8 HLA-matched pairs therefore benefits White patients and disadvantages patients of color, but removing this preference might result in higher rates of graft failure. Attempts to balance these competing considerations raise ethical questions about justice and beneficence.

Another ethical question in HSPC transplantation revolves around compensation or incentives for donation. Increasing the number and availability of HSCP donors would improve the probability of identifying an appropriate unrelated match for patients in need of a transplant, but the 1984 National Organ Transplant Act (NOTA) banned the sale of bone marrow and organs, making the provision of financial incentives to donate illegal (98th Congress, 1983). Nonetheless, debates over the ethics of providing incentives to encourage the donation of bone marrow and HSCs persist among bioethicists and health economists. In an effort to reduce disincentives to donate, the federal government offers up to 1 work week of leave for federal employees who donate bone marrow, and most states have followed suit for state employees (Lacetera et al., 2014). Some states also offer tax deductions for nonmedical donation-related costs, and there is some evidence that these types of legislation do lead to modest increases in donation rates (Lacetera et al., 2014).

Although removing disincentives to donation is generally considered ethically acceptable, there is more debate about whether offering financial incentives for donation equates to a morally problematic commodification of the human body. In 2011, the 9th Circuit held in *Flynn v. Holder* that compensation for the collection of PBSCs does not violate NOTA's ban on compensation (Cohen, 2012). In response, a coalition of cell therapy organizations published a statement arguing that this decision would mean that donors would no longer be motivated by altruism, and that people seeking to sell PBSCs might withhold important health information (Be the Match, 2012). After a regulatory back-and-forth over the status of PBSCs, HHS withdrew a proposed rule that would have effectively reversed *Flynn v. Holder,* so the current state of the law allows compensation for PBSCs (Todd, 2017).

Genetic Hematologic Disease: The Case of Sickle Cell Disease

Although Linus Pauling declared sickle cell disease (SCD) to be the first "molecular disease" (i.e., the first disease understood at the molecular level) in 1949, and it has long been considered an ideal target for gene therapy given that it is predominantly caused by a single mutation in the HBB gene and its phenotypic consequences are in a circulating cell type, developing a cure has not been as straightforward as hoped (Pauling et al., 1949). Though the presentation of SCD can vary significantly, clinical effects include anemia, painful vaso-occlusive crises, acute chest syndrome, splenic sequestration, stroke, chronic pulmonary and renal dysfunction, growth retardation, and premature death (OMIM, n.d.a.).

Standard treatment for SCD consists primarily of preventative and supportive care, including prophylactic penicillin, opioids for severe chronic pain, hydroxyurea, and transfusion therapy (Yawn et al., 2014). Such care has dramatically increased the life expectancy of those living with SCD (median survival in the United States is in the mid- to late 40s) (Wailoo, 2017; Ballas et al., 2016; Prabhakar et al., 2010). At the same time, this care costs more than $35,000 annually, and many patients have difficulty accessing such high-quality care, particularly adequate pain management (Bergman and Diamond, 2013; Haywood, 2013; Haywood et al., 2009; Kauf et al., 2009; Smith et al., 2006). Until recently, the only evidence-based cure for SCD and beta-thalassemia major was allogeneic hematopoietic cell transplantation (HCT), which comes with significant costs and risks (Bhatia and Walters, 2008).

Despite the fact that SCD is one of the most common genetic diseases worldwide and it was the first genetic disease to be molecularly defined, it has received relatively little research funding over the years, an observation that has been a frequent subject of critique (Farooq et al., 2020; Demirci et al., 2019; Benjamin, 2011; Smith et al., 2006; Scott, 1970). In contrast to better-funded diseases, such as cystic fibrosis and Duchenne muscular dystrophy, which are more common in White individuals of European descent, in the United States, SCD predominantly affects non-Hispanic Black and Hispanic populations, including 1 in 365 Black individuals and 1 in 16,300 Hispanic individuals (OMIM, n.d.b., n.d.c.; CDC, 2022). This disparity in research funding despite disease prevalence is part of the larger story of the impacts of structural racism in the United States and on its medical system (The New York Times, 2019; IOM, 2003; HHS and AHRQ, 2003).

Furthermore, as noted previously, those of African and Hispanic ancestry are less likely to be able to identify a suitable match in the existing registries. Due to this difficulty, the improvements in treatment not focused on an HSPC transplant, and the risks of such a transplant, relatively few patients with SCD are treated with HSPC transplant (Yawn et al., 2014; Benjamin, 2011). Gene therapy delivered in the context of an autologous HSPC transplant offers the possibility not only of a safer cure but also broader access by eliminating the need to identify a matched donor.

Recently, the promise of regenerative medicine and gene therapy for genetic hematologic disease appears to be coming to fruition (Ledford, 2020; Stein, 2020; Kolata, 2019). While a number of approaches are currently in various stages of preclinical and clinical research, two promising clinical trials involve the induction of fetal hemoglobin (rather than direct correction of the disease-causing mutation in the HBB gene) (Demirci et al., 2019). Fetal hemoglobin is the predominant globin type in the second and third trimester fetus and for the first few months of life, at which point production shifts from fetal to adult hemoglobin. It has long been recognized that SCD does not present until after this shift occurs (Watson et al., 1948). Furthermore, some patients with the causative SCD mutation are nonetheless asymptomatic, due to also having inherited hereditary persistence of fetal hemoglobin mutations (Stamatoyannopoulos et al., 1975). These findings and others suggested that inducing fetal hemoglobin, even in the presence of a faulty HBB gene, could mitigate the disease.

The first trial uses a viral vector to introduce into autologous bone marrow a short hairpin RNA (shRNA) that inhibits the action of the BCL11A gene. BCL11A is an inhibitor of fetal hemoglobin, so when BCL11A is inhibited, fetal hemoglobin can be produced (Esrick et al., 2021). The second trial—the first published study to use CRISPR to treat a genetic disease—includes both patients with SCD and with transfusion-dependent ß-thalassemia (Frangoul et al., 2021). In this trial, CRISPR-Cas9 is used to target the BCL11A gene to affect the same de-repression of fetal hemoglobin as in the first trial. Both trials, which have collectively enrolled more than 15 patients, have reduced or eliminated the clinical manifestation of disease in all patients thus far, though it remains to be seen how long-lasting this effect will be. However, the first trial was recently suspended after participants in the first trial and a related trial developed acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) (Liu, 2021); an investigation is under way regarding the cause of the AML and MDS. Marketing of a treatment for transfusion-dependent ß -thalassemia currently approved and available in the European Union (EU) was also suspended, as that treatment is manufactured using the same vector (BB305 lentiviral vector) used in the current trials, and it is possible that the vector is the source of the serious adverse events in the research participants.

Further challenges remain, including technical challenges, such as the possibility that gene editing tools, as they are derived from bacterial systems, will provoke an immune response; and concerns about financial access, given the anticipated cost of such curative therapies (ICER, 2021; Kim et al., 2018). In addition, despite the technical ease of the technology and designing new nucleic acid targets, intellectual property protecting CRISPR has, to date, narrowed the number of developers actively pursuing CRISPR-based clinical trials (Sherkow, 2017). At the same time, this new technology might also solve a number of ethical issues around HSPC transplants, including by expanding biological access to HSPC transplant and mitigating the concerns raised by the creation of "savior siblings" for HLA-matched cord blood transplantation for older siblings (Kahn and Mastroianni, 2004).

Unproven Cell-Based Interventions

A long-standing challenge in the field of regenerative medicine is the DTC marketing of unproven cell-based interventions. Since at least the 2000s, unscrupulous scientists and health professionals in the United States and internationally have been offering "stem cell therapy" at significant cost, often to vulnerable individuals, and without a legitimate scientific or medical basis (Knoepfler and Turner, 2018; Murdoch et al., 2018; Regenberg et al., 2009; Enserink, 2006). From 2009 to 2016, the number of such clinics in the United States doubled annually (Knoepfler and Turner, 2018). While the clinics look legitimate, their claims are fantastical, promising to treat or cure everything from knee pain to Parkinson's disease. Such clinics are often vague about the cell sources involved in the interventions offered, but sometimes they claim to use bone marrow, cord blood, embryonic stem cells, and iPSCs, as well as other types of autologous adult stem cells (e.g., adipose, olfactory) and a range of other cell types, cell sources, and cell mixtures (Murdoch et al., 2018). While such interventions launch from legitimate science and scientific potential, the claims exceed and diverge from what is proven. The interventions are at best very expensive placebos and at worst could cause serious harm or death (Bauer et al., 2018).

Over time, attempts have been made to rein in these clinics by the FDA, the Federal Trade Commission (FTC), the ISSCR, individual customers and their lawyers, and others, but these attempts have faced a number of challenges (Pearce, 2020). The ISSCR, the primary professional society for those engaged in regenerative medicine, has struggled for years against such clinics. Early on, they attempted to establish a mechanism to publicly vet these clinics, though the effort was abandoned in part due to push back from the clinics' lawyers (Taylor et al., 2010; personal communication from ISSCR Leadership, n.d.). In part because the majority of US-based clinics offer autologous interventions (removing and then reintroducing the patient's own cells), the FDA struggled to clarify the line between medical practice and their regulatory authority. The FDA began issuing occasional warning letters to these clinics starting in 2011, though the letters

were issued infrequently (Knoepfler and Turner, 2018). Under this relatively weak enforcement, the market expanded dramatically, and pressure increased on the FDA to take meaningful action (Knoepfler, 2018; Turner and Knoepfler, 2016).

In late 2017, the FDA took several significant steps to curtail these clinics, including using U.S. marshals to seize product from a California clinic, bringing a lawsuit against a Florida clinic, and publishing largely celebrated finalized guidance outlining a risk-based approach to the regulation of regenerative medicine products (FDA, 2019; Pew Research Center, 2019). The following year, the FTC took independent action against clinics making false claims about their interventions, and Google banned advertising for "unproven or experimental medical techniques such as most stem cell therapy, cellular (non-stem) therapy, and gene therapy" (Biddings, 2019; Fair, 2018). In 2019, the FDA won their case against US Stem Cells in Florida, significantly strengthening their ability to regulate these clinics (Wan and McGinley, 2019). Following the establishment of clear regulatory authority over at least a subset of clinics, FDA has begun to step up its enforcement (Knoepfler, 2020; Wan and McGinley, 2019; FDA, 2018). Increased action is anticipated following the end of the 3-year grace period established in the 2017 guidance, though there is some concern about the capacity of the agency to make significant headway against the more than 600 clinics now in operation—a worry bolstered by a 2019 study suggesting that despite increased enforcement, the unproven stem cell market seems to have shifted rather than contracted (Knoepfler, 2019; Pew Research Center, 2019). What seems clear is that it will take a collective and multipronged approach to ensure that the cell-based interventions to which patients have access are safe and effective (Lomax et al., 2020; Pew Research Center, 2019; Master et al., 2017; Zarzeczny et al., 2014).

Cross-Sectoral Footprint

The cross-sectoral analysis is structured according to sectors (see *Figure 2*) and domains (science and technology, governance and enforcement, end-user affordability and insurance reimbursement [affordability and reimbursement], private companies, and social and ethical considerations). The sectors described subsequently are intended to be sufficiently broad to encompass a number of individuals, groups, and institutions that have an interest or role in regenerative medicine. Health care is the primary nonprofit actor of interest, and so in this structure, "health care" has replaced "nonprofit," though other nonprofit actors may have a role in this and other emerging technologies, and, of course, not all health care institutions are nonprofits.

Today, many regenerative medicine technologies are researched, developed, and promoted by a scientific-industrial complex largely driven by market-oriented goals. The development of various components of regenerative medicine may be altered by differing intellectual property regimes. This larger ecosystem is also embedded in a broad geopolitical context, in which the political and the economic are deeply intertwined, shaping national and regional investment and regulation. The political economy of emerging technologies involves and affects not only global markets and regulatory systems across different levels of government but also nonstate actors and international governance bodies. Individuals and societies subsequently adopt emerging technologies, adjusting their own values, attitudes, and norms as necessary, even as these technologies begin to shape the environments where they are deployed or adopted. Furthermore, individual and collective interests may change as the "hype cycle" of an emerging technology evolves (Gartner, 2022). Stakeholders in this process may include scientific and technological researchers, business firms and industry associations, government officials, civil society groups, worker

FIGURE 2 | Sectors for Cross-Sectoral Analysis

SOURCE: Developed by authors.

safety groups, privacy advocates, and environmental protection groups, as well as economic and social justice–focused stakeholders (Marchant et al., 2014).

This intricate ecosystem of stakeholders and interests may be further complicated by the simultaneous introduction of other technologies and platforms with different constellations of ethical issues, modes of governance, and political economy contexts. In the following sections, this ecosystem is disaggregated and organized for ease of presentation. It is important to keep in mind that there are entanglements and feedback loops between and among the different sectors, such that pulling on a single thread in one sector often affects multiple areas and actors across the broader ecosystem.

Cross-Sectoral Analysis

Academia

For the purposes of this case study, the primary actors within the academic sector are academic and clinical researchers and the professional societies that represent them.

- *Science and technology:* This case involves a tremendous amount of research and development that has taken place in and grown out of academia, including preclinical and clinical HSPC transplant research; human ESC, EGC, and iPSC research; and genome editing.
- *Governance and enforcement:* Current work at research institutions is governed by IRBs and REBs, stem cell research oversight committees, and institutional animal care and use committees, among other bodies. In addition, research funding bodies, academic publication standards, and scientific and professional societies (i.e., self-regulation) also have a role to play—in particular, the ISSCR and its role in the governance of pluripotent stem cell research and in addressing clinics offering unproven cell-based therapies. The National Academies of Sciences, Engineering, and Medicine played a critical role in the governance of ESC research, particularly from 2005 until 2010.
- *Affordability and reimbursement:* While not strictly a matter of patient affordability, it is important to reiterate, as noted previously, that funding available for academic research has disproportionately benefited those with diseases such as cystic fibrosis and Duchenne muscular dystrophy, which are more common in White individuals of European descent, compared to SCD, which in the United States is more prevalent among non-Hispanic Black and Hispanic populations (Farooq et al., 2020; Demirci et al., 2019; Benjamin, 2011; Smith et al., 2006; Scott, 1970).
- *Private companies:* Academic–industry research partnerships, including industry-funded clinical trials, are involved in this space; for example, the CRISPR-based clinical trial was funded by two biotechnology companies (Frangoul et al., 2021). Such partnerships are often predicated on exclusive intellectual property licenses to "surrogate licensors" (Contreras and Sherkow, 2017).
- *Social and ethical considerations:* Extensive bioethics literature exists on the ethical, legal, and societal issues raised by human subjects research, first-in-human clinical trials, stem cell research, clinics offering unproven cell-based interventions, genome editing, health disparities, and structural racism. Much has also been written on the role of intellectual property and data and materials sharing in the context of human tissue research and genome editing.

Health Care

Given the focus of CESTI on health and medicine, for the purpose of this case study, the primary actors within the nonprofit sector are those involved in health care, including hematopoietic stem and progenitor cell registries, health insurance companies, and medical profession associations.

- *Science and technology:* HSPC transplants have been clinically available for decades, but research and improvement in this space continue.
- *Governance and enforcement:* Today, the WMDA serves as the accrediting body for registries and promulgates regulations and standards to which the registries adhere on issues like the organization of a registry, the recruitment of volunteer donors, and the collection and transportation of HPCs (WMDA, 2022; Hurley et al., 2010). These standards represent the minimum guidelines for registries, which "demonstrate their commitment to comply with WMDA Standards through the WMDA accreditation process" (Hurley et al., 2010). Other groups involved in the governance of aspects of HSPC transplant are included in *Table 1*.

  It is important to note that the "nonprofit" label in this context is somewhat fraught. Many (perhaps most) health care organizations are very much in the business of making money. One of these is the NMDP, which operates Be the Match, and which has diversified its portfolio over time, including the launch in 2016 of Be the Match BioTherapies, which partners with dozens of cell and gene therapy companies, supplying cells and services to "advance the development of life-saving cell and gene therapies" (Be the Match, 2021a,b).

  The FDA generally has authority to regulate bone marrow transplantation through its oversight of bone marrow itself as a human cellular tissue product (HCT/P) and, therefore, a "biologic" (U.S. Code § 262, n.d.). Typically, biologic

TABLE 1 | HSC Registries

Organization	Acronym	Year Founded	Role	Activities
Worldwide Network for Blood & Marrow Transplantation	WBMT	2007	Coordination	• Coordination, communication, and advocacy
World Marrow Donor Association	WMDA	1994 (Petersdorf, 2010)	Standards and accreditation	• Registry operations (Hurley et al., 2010)
Joint Accreditation Committee-ISCT (International Society for Cellular Therapy) and EBMT (European Group for Blood and Marrow Transplantation)	JACIE	1998	Standards and accreditation	• Collection/harvest centers
Foundation for the Accreditation of Cellular Therapy	FACT	1996	Standards and accreditation	• "general cellular therapy manufacturing and administration • processing and clinical use of hematopoietic progenitor cells obtained from bone marrow or peripheral blood • umbilical and placental cord blood banking" (Maus and Nikiforow, 2017)
National Marrow Donor Program	NMDP	1986	Registry	• Operate the Be The Match registry
Center for International Blood and Marrow Transplant Research	CIBMTR	2004	Research, best practices	
Asia-Pacific Blood and Marrow Transplantation Group	APBMT	1990	Professional society	
American Society for Transplantation and Cellular Therapy	ASTCT	1993	Professional society	• Practice guidelines • Advocacy

SOURCE: Developed by authors.

products are required to submit to the FDA's premarket review process, including the filing of an investigative new drug application and clinical trials. With that said, the FDA has exempted certain types of bone marrow transplantation procedures from such review: namely, bone marrow products that are used in a same-day surgical procedure and those that are only "minimally manipulated" (FDA, 2020). Importantly, while the FDA's minimally manipulated exception broadly applies to autologous therapy, including the sort of therapy private cord blood banks are intended to plan for, it only applies to allogenic therapy if derived from a "first-degree or second-degree blood relative"; allogenic therapy using cells from more distant relatives requires the FDA's premarket review (FDA, 2020).

Cord blood matching and donor priority is controlled by the NMDP and regulated by the FDA (CFR, 2012). However, because cord blood therapy is almost always allogenic and usually from anonymized donors unrelated to the patient, cord blood HSPC transplant generally does not fulfill the FDA's "minimal manipulation" exemptions for HCT/P (FDA, 2020). As such, a total of eight public cord blood banks have applied for, and received, approval from the FDA for their cord blood products (FDA,

2022). Generally, public banks are held to transparent, rigorous storage and quality standards that do not apply to private banks, leading to lower overall quality of cord blood in private banks (Shearer et al., 2017; Sun et al., 2010; Committee on Obstetric Practice, 2008).

The American Academy of Pediatrics has taken a position on private versus public cord blood banks and supports public banking, as do the American Medical Association and the American Congress of Obstetricians and Gynecologists (AMA, n.d.; ACOG, 2019; Shearer et al., 2017).

- *Affordability and reimbursement:* Both public and private insurers in the United States tend to distinguish autologous from allogenic bone marrow therapies, covering autologous transplantation for some indications and allogenic transplantation for others (CMS, 2016).

  Leaving aside the broader issues of health insurance and health care affordability in the United States, annual and lifelong care costs for genetic hematologic diseases like SCD and thalassemia are considerable—the yearly cost of standard of care for a patient with SCD is more than $35,000 (Kauf et al., 2009). Novel therapies—both pharmacologic and those based on HSPC transplants—are anticipated to be extraordinarily expensive, if proven safe and effective. For example, the drugs Oxbryta and Adakveo, approved in 2019 for treating SCD, are estimated to cost $84,000 and $88,000 per year, respectively (ICER, 2021; Sagonowsky, 2020). CART-T cell therapy, which as another novel, genetically modified cell-based therapy may be a reasonable bellwether for the cost of the SCD therapies described previously, costs at least $373,000 for a single infusion before hospital and other associated costs (Beasley, 2019). Many patients suffering from these diseases are from historically marginalized and underserved populations that tend to have lower levels of income. In addition, as therapies become more bespoke, scaling will increasingly become a challenge, from both a regulatory and delivery perspective. However, these delivery challenges may also open new business opportunities.

  While donation of cord blood to a public bank is free to the donor, costs associated with private banking include a collection fee ($1,350–$2,300) and annual storage fees ($100–$175 a year), which are unlikely to be covered by health insurance (Shearer et al., 2017).

- *Private companies:* Many private companies advertise private cord blood banking to new parents as a form of biological insurance; however, the costs of collection and storage are not generally covered by medical insurance (private companies offering unproven cell-based interventions are included under the private sector rather than health care).
- *Social and ethical considerations:* Significant literature exists on health disparities and racism in medicine, including their impact on patients with SCD in particular. As noted previously, the likely high costs of these therapies raise serious concerns about access. There is also literature on ethical issues raised by the private cord blood market.

Private Sector

For the purposes of this case study, the primary actors within the private sector are companies involved in basic and translational regenerative medicine research and clinics offering unproven cell-based interventions.

- *Science and technology:* Many private biotechnology companies are involved in regenerative medicine and genome editing research and development. A recent analysis predicted that the global CRISPR genome editing market (including CRISPR products, applications, and end-users) could grow from about $850 million in 2019 to $10 billion by 2030 (BIS Research, n.d.). In the United States, there are more than 600 clinics offering unproven cell-based interventions.
- *Governance and enforcement:* The ISSCR attempted to establish a mechanism to publicly vet clinics selling unproven cell-based interventions, though the effort was ended in part due to push back from the clinics' lawyers (personal communication from ISSCR leadership, n.d.; Taylor et al., 2010). In part because the majority of U.S. clinics offer autologous interventions (removing and then reintroducing the patient's own cells), the FDA has struggled to clarify the line between medical practice and their regulatory authority in this space. Under relatively weak enforcement, the market expanded dramatically.

  In late 2017, the FDA took several significant steps to curtail these clinics, including using U.S. marshals to seize product from a California clinic, bringing a lawsuit against a Florida clinic, and publishing largely celebrated finalized guidance that outlined a risk-based approach to the regulation of regenerative medicine products (FDA, 2019; Pew Research Center, 2019). The following year, the FTC took independent action against clinics making false claims about their interventions, and Google banned advertising for "unproven or experimental medical techniques such as most stem cell therapy, cellular (non-stem) therapy, and gene therapy" (Biddings, 2019; Fair, 2018). In 2019, the FDA won their case against U.S. stem cells in Florida, significantly strengthening their ability to regulate these clinics (Wan and McGinley, 2019). Following the establishment of clear regulatory authority

over at least a subset of clinics, the FDA has begun to step up its enforcement (Knoepfler, 2020; Wan and McGinley, 2019; FDA, 2018).

- *Affordability and reimbursement:* Unproven cell-based interventions can cost anywhere from several thousand dollars to tens of thousands of dollars (Regenberg et al., 2009). These costs are not covered by insurance. Patients have engaged in public fundraising campaigns, including on crowdfunding sites, to raise the money necessary to access the unproven intervention.
- *Private companies:* There are far too many companies offering unproven cell-based interventions to list, though a recent accounting can be found in a supplemental table to Turner and Knoepfler, 2016.
- *Social and ethical considerations:* Many have written about the ethical and policy issues raised by DTC unproven cell-based interventions and private cord blood banks, including issues related to truth-telling, taking advantage of historically marginalized and underserved individuals, and significant financial costs and physical risk in the absence of demonstrable benefit, among other issues.

Government

For the purposes of this case study, the primary actors within the government sector are the FDA, the FTC, the NIH, and other regulatory bodies.

- *Science and technology:* The federal government, and especially the NIH, has funded a tremendous amount of the research outlined in this case and is a critical part of the biotechnology research and development ecosystem.
- *Governance and enforcement:* NOTA banned the sale of bone marrow and organs (98th Congress, 1983). Nonetheless, debates over the ethics of providing incentives to encourage the donation of bone marrow and HSCs persist among bioethicists and health economists. In an effort to reduce disincentives to donate, the federal government offers up to 1 week of leave for federal employees who donate bone marrow, and most states have followed suit for state employees. Some states also offer tax deductions for nonmedical donation-related costs, and there is some evidence that these types of legislation do lead to modest increases in donation rates (Lacetera et al., 2014).

  Regarding pluripotent stem cell research, current governance of federally funded research includes the Dickey-Wicker Amendment and NIH's 2009 guidelines, which remain in effect.

  A notable approach to governance of cell-based interventions in Japan and elsewhere is the implementation of a sunset provision for therapy approvals (Maeda et al., 2015). Combined with post-market surveillance, this mechanism creates a default that a provisionally approved therapy comes off the market after a defined period of time unless proven safe and effective. While this model has faced challenges in Japan due to the pressure to keep approved interventions on the market, it has been more successful than similar provisions implemented for drug approvals in Europe (Maeda et al., 2015).

  A significant challenge of HSPC transplants, combined with CRISPR and other technologies going forward, will be monitoring for late effects and the governance structures associated with that process.
- *Affordability and reimbursement:* Proven HSPC transplants may be covered by public funding schemes; unproven cell-based interventions are not.
- *Private companies:* N/A
- *Social and ethical considerations:* Concerns in this sector include the disproportionate lack of research funding available for genetic hematologic disease, such as SCD and thalassemia; public funding of embryonic stem cell research; and the role of the public in decision-making about research that bears on questions of human meaning (Frangoul et al., 2021).

Volunteer/Consumer

For the purposes of this case study, the primary actors within the volunteer/consumer sector are patients and consumers seeking regenerative medicine–based solutions to their medical concerns. It is important to keep in mind that many members of "the public" nationally and internationally never have the opportunity to be patients or consumers of emerging technologies, and so do not show up in the following analysis. These members of the public may nonetheless be affected by the development, deployment, and use of such technologies, and those impacts should be taken into account.

- *Science and technology:* There are few approved regenerative medicine–based therapies in the United States or internationally beyond those described previously, though there are many clinical trials under way.
- *Governance and enforcement:* The ISSCR attempted to establish a mechanism to publicly vet clinics selling unproven cell-based interventions, though the effort was abandoned in part due to push back from the clinics' lawyers (Personal communication from ISSCR leadership, n.d.; Taylor et al., 2010). The ISSCR does have educational materials available for the public on this topic (A Closer Look at Stem Cells, 2022).

  In 2018, the FTC took independent action against clinics making false claims about their interventions, and Google banned advertising for "unproven or experimental medical techniques such as most stem cell therapy, cellular

(non-stem) therapy, and gene therapy" (Biddings, 2019; Fair, 2018). Reducing access to information about these clinics could lead to decreased use by customers. Direct action against the clinics by the FDA is described in the "Private Sector" section.

- *Affordability and reimbursement:* As noted previously, unproven cell-based interventions can cost anywhere from several thousand dollars to tens of thousands of dollars (Regenberg et al., 2009). These costs are not covered by insurance. Patients have engaged in public fundraising campaigns, including on crowdfunding sites, to raise the money necessary to access the unproven intervention.
- *Private companies:* Clinics offering unproven cell-based interventions and private cord blood banks are covered in the "Health Care" and "Private Sector" sections.
- *Social and ethical considerations:* There are significant concerns about safety, therapeutic misconception among consumers, and use in children and other historically marginalized and underserved groups whose members lack the capacity to consent.

Ethical and Societal Implications

What is morally at stake? What are the sources of ethical controversy? Does this technology/application raise different and unique equity concerns?

In outlining the concerns of the authors in terms of the use of this technology, we considered the following ethical dimensions, as outlined in the recent National Academies of Sciences, Engineering, and Medicine report, *A Framework for Addressing Ethical Dimensions of Emerging and Innovative Biomedical Technologies: A Synthesis of Relevant National Academies Reports* (NASEM, 2019).

- Promote societal value
- Minimize negative societal impact
- Protect the interests of research participants
- Advance the interests of patients
- Maximize scientific rigor and data quality
- Engage relevant communities
- Ensure oversight and accountability
- Recognize appropriate government and policy roles

It is important to keep in mind that different uses of this technology in different populations and contexts will raise different constellations of issues. For example, HSPC transplants for malignancies raise different issues than the same therapy for SCD; both of these are of course quite different than the many uses of unproven cell-based interventions in patients outside standard clinical care. Some of the specific concerns might include the following:

- How should the risks and benefits of first-in-human clinical trials be weighed?
- How should the risks/benefits of (ideal) existing standards of care be balanced against the risks/benefits of novel attempts at cures?
- What should be the role of the public in the governance of research and applications that bear on questions of human meaning?
- How can regulators more effectively address clinics offering DTC unproven cell-based interventions, including issues related to truth-telling, taking advantage of historically marginalized and underserved people, and significant risks in the absence of demonstrable benefit?
- In the DTC marketplace, how can the safety of interventions offered be ensured, and how can therapeutic misconception among consumers, including parents of sick children, be avoided?
- How can and should historical and ongoing health disparities, structural racism, and racism in medicine be taken into account in the assessment of new technologies?
- What are the benefits and challenges of intellectual property and data and materials sharing in the context of human tissue research and genome editing?
- What is the role of science and data in the governance of the private cord blood market?
- What is the appropriate governance response when the relevant regulatory authority lacks sufficient funds to execute its authority?

Beyond Regenerative Medicine

As noted at the beginning of this case, regenerative medicine, its applications, and its implications are very broad. The same work that enabled the development of iPSCs, and therefore the matching of cellular therapies to particular individuals, has also led to improved understanding of the processes of cellular aging and senescence (Svendsen, 2013). Despite the significant increase in average human lifespan, there has yet to be an equivalent increase in the human health span (Christensen et al., 2009). Diseases and conditions associated with age contribute to this discrepancy, causing older adults to spend more time in physiological deficiency, and have encouraged the scientific community to develop therapies that slow or even reverse the effects of aging (Beyret et al., 2018). The discovery of the ability to reverse cellular fate has encouraged researchers to better understand the biological process of aging, which could provide insight into the development of therapies to extend healthy longevity (Takahashi and Yamanaka, 2006). Several rejuvenation methods involving blood factors, metabolic changes, senescent cell ablation, and differing levels of cellular reprogramming are currently under investigation (Mahmoudi et al., 2019). Specific areas of interest include further research into the role of telomere shortening in

cellular senescence and the ability of telomerase to counteract such shortening and extend cellular lifespan as well as applications of reprogramming aged stem cells into iPSCs or directly into tissue-specific stem cells (Spehar et al., 2020; Bernadotte et al., 2016; Nobel Prize, 2009; Bodnar et al., 1998). Moreover, genetic modifications to rejuvenate or extend the therapeutic effects of aged stem cells could enhance treatment capabilities for a multitude of diseases, including metabolic and neurodegenerative disorders (Navarro Negredo et al., 2020; Zhou et al., 2020; Ahmed et al., 2017).

Despite recent advances in the field of regenerative medicine, many challenges remain. Although the ability to reprogram cells in vitro is well documented, more work is needed to establish best practices for in vivo manipulation and to assess long-term outcomes in nonhuman animals before such therapies can be translated to the clinic (Beyret et al., 2018; Mertens et al., 2018). In addition, tampering with the natural safeguards that exist to prevent cellular reprogramming can lead to unintended consequences such as tumor growth (Brumbaugh et al., 2019; Abad et al., 2013). However, recent work to counteract the negative effects of aging shows promise that such challenges can be overcome. For example, Ocampo et al. explored partial cellular reprogramming by inducing temporary expression of the Yamanaka factors, *Oct4*, *Sox2*, *Klf4*, and *c-Myc* (OSKM) in vivo in mice (Ocampo et al., 2016). The results of their experiments demonstrated decreased cellular and physiological signs of aging; increased lifespan of progeroid mice; and shortened recovery time for older mice with metabolic diseases and muscle injury, all without the side effect of tumor growth. Continued investigation into the potential of regenerative medicine gives scientists the opportunity to better understand the aging process and to perhaps translate innovative therapies into the clinic to counteract the maladies that accompany old age.

Visioning

As alluded to previously, it is possible to foresee numerous future scenarios regarding the evolution of regenerative medicine. In an effort to probe the kinds of worries that the authors have about the trajectories of emerging technologies, to expand the range of lessons learned from each case, and ultimately to "pressure test" the governance framework, the authors have developed a brief "visioning" narrative that pushes the technology presented in the core case 10–15 years into the future, playing out one plausible (but imagined) trajectory. The narrative was developed iteratively in collaboration with a case-specific working group, with additional feedback from all members of CESTI. All reviewers are acknowledged in the back matter of this paper. Each narrative is told from a particular perspective and is designed to highlight the social shifts that shape and are shaped by the evolving technology.

Regenerative Medicine Case Visioning Narrative

Perspective: Potential but conflicted off-label user

Background

It is 2035. After the COVID-19 pandemic, mRNA delivery technology has expanded significantly. Scientists are now readily able to temporarily (and with some genome editing techniques, permanently) express synthetic proteins in a wide variety of cell types using lipid nanoparticle (LNP)-encased synthetic mRNA molecules. The mRNA mixture is delivered via simple intramuscular injection or intravenous infusion. In addition, researchers have made significant advancements in directing mRNA-LNPs to specific tissues.

Meanwhile, research on cellular rejuvenation has yielded dramatic insights into mechanisms of "turning back the cellular clock" via partial reprogramming. Researchers can now rejuvenate cellular function and growth. This can be accomplished by the transient (and careful) expression of the four Yamanaka factors—*Oct3/4*, *Sox2*, *Klf4*, and *c-Myc*—in a wide variety of human cell types. Researchers can now also provide safeguards to avoid the risk of tumor development. Early research in animals using a combination of mRNA-LNP and rejuvenation technology has produced startling insights. The technology appears to not only reverse aging in animals but also seems to extend youthful life—in some instances, for example, youthful life in treated mice was up to twice as long as in nontreated controls. Upon publication of these results, testing on extending the breeding life of racehorses quickly began. The implications for the technology are vast.

This marriage of mRNA delivery technology and cellular rejuvenation research has yielded two therapeutics, developed by LioRNA Therapeutics, which can dramatically reverse age-related conditions. A variant of this technology was first approved for use in pets. The first, an intramuscular shot delivered once every 5 to 10 years, rejuvenates T cell production to combat age-related deterioration; it is, essentially, an immune booster for aging. The second is a therapy designed to speed up healing of certain injuries in a variety of tissue types otherwise similarly affected by age-related deterioration. The results are astounding. Injuries that would have taken months to heal in older populations now take weeks; infections that would have claimed the lives of elderly patients are now easily surmountable with standard treatment. In addition, both therapies—as animal models indicated—seem to reverse the effects of aging. Whether they extend patients' lifespans is, as of 2035, unclear but expected by many. Notably, however, LioRNA's therapies do not cross the blood–brain barrier. The therapies are approved in the United States and the European Union in 2031.

The popular press—with help from LioRNA's marketing team—hails the therapy as a "miracle" and a fulfillment of decades of promises of regenerative medicine. Scientists advocate the

science behind the treatment through popular scientific outlets including TEDx talks and conferences, as well as YouTube and other forms of social media. The therapy is also immediately co-opted by professional athletes seeking to recover more quickly from their injuries. Amateur athletes in a variety of injury-inducing sports follow suit and post their accomplishments online. Body-builders have also adopted the therapy off-label to "naturally and undetectably" increase the benefits of strenuous exercise without the risk of injury. This extension of the therapy beyond its relatively narrow intended use raises its prestige, and the general public takes an interest. A number of adventurous younger people and wellness seekers get the shot off-label for enhancement purposes and brag about their newfound vigor on social media. This includes a number of celebrities and social media influencers.

In addition, because of a substantial global excess of idle mRNA LNP manufacturing facilities, left over from their dramatic expansion in 2022 to end the COVID-19 pandemic, a number of "wildcat" wellness clinics begin to attempt to copy LioRNA's therapies to offer them as an "anti-aging cure." Safety concerns related to these clinics abound.

By 2035, off-label use of LioRNA's therapies (and copycats from various clinics) begin to take hold in various segments of the population. The treatment is especially popular in high-income areas where anti-aging interventions are popular (e.g., Los Angeles and South Korea). Some of the interest in the technology may also be related to public financial austerity programs around the world with respect to health care for the elderly. Seeing a tremendous increase in the cost of gerontological care, especially as the populations of high-income countries age, well-off governments around the world have begun to restrict a variety of health care interventions for the elderly. Not knowing whether they will have adequate care when they are older, taking LioRNA's therapy (or getting it from a wildcat clinic) is, to many, a sensible "hedging of their bets."

While the technology has not yet transformed society, it is on the cusp of doing so. Patients (and practitioners, some of whom are ardent advocates of the technology) are faced with a number of issues as they navigate a series of choices about whether to use LioRNA's anti-aging therapy for purposes beyond its narrow label.

Scott Oliveri, a 59-year-old, healthy, widowed, middle-class heating, ventilation, and air conditioning engineer in Ohio with two sons, is faced with many of these issues. Scott has seen the results of numerous friends—his peer age group—taking LioRNA's therapy, some on-label, others off. The increased physical activity in Scott's peer group—largely, greater participation in recreational sports—has induced a form of peer pressure to obtain the therapy or be left out of these popular activities. In addition, Scott desires—but is conflicted about—receiving the therapy so he can continue to work and delay his retirement. Scott is both concerned about the longevity of a social safety net for the elderly (e.g., Medicare), and philosophically uncomfortable with the safety net. He finds assessing his insurance coverage prior to treatments to be complicated.

Gerontological Disease Management

The existence of LioRNA's therapy has begun to revolutionize gerontological disease management. The ethics of its use in patients among the medical community is hotly contested. After watching patients senesce or succumb to accidents, many practitioners have now begun advocating patients get the rejuvenation shot. In particular, the unintended effect of LioRNA's therapy on muscle production seems to miraculously stave off aging-related sarcopenia. As a consequence, in the United States, many physicians prescribe the treatment off-label or, even where indicated, prescribe it for the primary purpose of achieving rejuvenation benefits in their patients. In other instances, when physicians attempt to discuss healthy living and healthy aging with their patients, they are often cut short by discussions surrounding getting the shot, even for aging-related diseases for which the shot has little effect.

Use of the therapy, on- or off-label, is complicated by the fact that the therapies do not cross the blood–brain barrier. As a consequence, the effect of the technology on age-related dementia and other mental impairments is, as of 2035, entirely unclear. Early data suggest a risk of differential aging: the number of older, healthy, and physically able patients with declining mental acuity appears to be high. Alarmingly, in a subset of patients, the therapy has differential effects across tissues (e.g., it is shown to successfully rejuvenate muscle, but does not have the same effect on an injured tendon), which results in severe chronic pain. This is discounted by some physicians but is a topic of significant concern for others. Scott is vaguely aware of these concerns, but, as informed by his peer group, he believes these "side effects" to be small. In addition, Scott's primary care physician, who he has seen for 20 years, is not a gerontological specialist and is not as up to date on these nuances of LioRNA's therapy as other colleagues.

Insurance Practice

Insurers are initially hesitant to widely cover the LioRNA therapies, and they only partially reimburse or cover the therapy (and only where the primary indication—age-related immune deficiencies and injury recovery—is present). Some insurers, however, seeing the enormous benefit of the therapy beyond its label (and its cost-effectiveness), and begin to mandate the treatment as top-line therapy before covering others, especially where "injury" is present, using an intentionally broad definition. Less desirable interventions, some of which are, by clinical estimations, inferior to mRNA anti-aging treatment, become second-line therapy, if used at all. In addition, some insurers have negotiated value-based agreements with LioRNA, which have proven remarkably successful for both LioRNA and some payers, especially those

covering aging populations. As a consequence, many patients, presented with their insurers' directives, are induced to choose the therapy for a wide variety of conditions even where they would not otherwise choose the treatment. Scott, however, is 59 years old and healthy and is below the age and indication cutoff for many of these incentive programs. He has had difficulty getting an answer from his insurer as to whether and what extent he would be reimbursed for treatment. Scott has heard that friends his age who have injured themselves playing recreational sports or otherwise by accident were entitled to full reimbursement from their insurers. Scott has joked that one "needs to get hurt to get insurance to pay for the shot."

Equity, Access, and Medical Tourism

Some uninsured patients, the "worried middle aged," and LioRNA enthusiasts begin to visit wildcat clinics in the United States for either cheaper versions of the shot or for certain modifications, including tissue targeting for reproductive issues. Given the safety profile of these compounded treatments, many are injured as a result; it is also unclear if the modified forms of the technology work as advertised, as the evidence is mixed. Other patients resort to anti-aging medical tourism where mRNA-LNP manufacturing capacity is most available (notably India, following the increase in manufacturing capacity post COVID-19 pandemic). This has the effect of raising the therapy's price globally and diminishing access to the poorest among a number of low- and middle-income countries, despite the increase in mRNA-LNP production capacity. This is lamented by a number of public health researchers who point out, correctly, that the world's poorest are the most negatively affected by aging relative to other groups. In this sense, differential access will likely have a significant and negative impact on health equity.

Biohacking

The popularity of LioRNA's therapy, and excess mRNA-LNP manufacturing capacity on a contract basis worldwide, has spurred a major biohacking movement. Biohackers are developing their own versions of the LioRNA therapies and also creating their modifications, both for disease-treatment and for enhancement purposes. Online, biohackers share mRNA sequences for synthesis, manufacture, and injection, including modifications pertaining to various age-related concerns (e.g., age-related vision loss). Some of these experiments appear to be successful. Others, however, are less so, including complications pertaining to cancer risk so studiously avoided in LioRNA's commercial products. Scott—otherwise unsure as to whether his insurer will cover the therapy—has been encouraged by one of his sons to visit a wildcat clinic to receive the therapy, on the premise that "it's cheaper" and that he doesn't "need to worry about insurance." Scott has also heard from his son that a hobbyist could make a hacked version for him. Scott is concerned about safety issues, some of which have been present in the news and on social media.

Social Context of Aging

LioRNA's technology, and its popularity, has made aging-related infirmities, once a normal facet of life, increasingly viewed as treatable maladies. Among the elderly and aging, aging-related health conditions are increasingly viewed with skepticism, in the same manner as contracting a communicable but preventable illness. There is peer social pressure to "get the shot," exacerbated by social and other electronic media. In addition, declining standards in elderly home care facilities is leveraged to encourage those who are aging to use LioRNA's treatments. Children of aging parents, worried about their care, are also pressuring their parents to use the therapy. Beyond all of this, there is a popular fear (yet to be appreciably realized) that the widespread use of the therapy will result in the diminishment of social safety nets for the elderly, including social security and Medicare. Scott is worried about these same issues and is cognizant of not wanting to be a burden on his children. As uptake of the therapy in his peer group increases, and he becomes more aware of memories of his parents aging, Scott is leaning toward accepting the therapy.

Sports

One of the therapy's first, as well as most public and prominent, uses is among professional athletes. Again, because one of the treatment's primary indications is rapidly healing from injury, physicians routinely prescribe the therapy to injured athletes. Some team physicians are selected, in part, on their willingness to prescribe the treatment to aging but valuable franchise athletes. All major professional sports see significant uptake of the therapy among their athletes, with significant pressure placed on the organizations' collective bargaining efforts regarding whether the therapy is properly characterized as an "enhancement." The therapy also becomes popular among amateur athletes who see it as a way to ward off injury. Scott, a sports enthusiast, is similarly moved by these efforts and their popularization online.

Regulation and Liability

The LioRNA treatments also challenge several precepts regarding regulation and consumer safety. On regulation, after years of developing guidelines regarding modular therapies (e.g., CAR-T and CRISPR-based therapies), the almost limitless indications and ease of modification of the therapies have challenged the FDA's ability to police the line between biologic and medical practice, and between a commercial manufacturer and a compounding laboratory. This is largely complicated by reluctance, both in the White House and in Congress, to allow the FDA to take a more active enforcement role in shutting down the wildcat clinics and biohackers dedicated to producing variants of LioRNA's treatments. Beyond this, the popularity of the therapy, and its introduction outside typical commercial channels in many cases, has complicated litigation concerning consumer safety.

Regenerative Medicine Case Study: Lessons Learned

Following are some of the lessons drawn from the preceding core case and visioning exercise that can inform the development of a cross-sectoral governance framework for emerging technologies focused on societal benefit.

- It is important to consider and articulate the role of the public in decision making regarding research and technology development bearing on questions of human meaning.
- Particularly in the absence of existing binding law or guidance, the National Academies (and other nongovernmental organizations) can play a critical role in governance, even when guidance is voluntary and nonbinding.
- Underfunded/understaffed agencies cannot effectively regulate every technology that falls within their mandate.
- The private sector can play a role in governance gaps (e.g., Google's action regarding stem cell clinic ads).
- The governance ecosystem around a technology will evolve with the technology.
- A state-by-state regulatory patchwork can stifle innovation and reduce or reshape the workforce in a field.
- Public perception of a technology may shift in response to positive clinical developments.
- Early, public success or failure can have an outsized impact on the development of a technology.
- Politics throws a spanner in the works.
- There is a critical need for trustworthy institutions at all stages and levels of technology governance.
- Special attention must be paid to research and technologies to which not all patients have access due to limits on knowledge or availability of genetic variation in the research, product, or patient (biological access).
- Special attention must be paid to the impact of compounding inequities (e.g., biological access and structural racism).
- Sometimes scientific and technological solutions can be found to ethical concerns.
- Special attention must be paid to technologies based on human tissues and data (i.e., human tissue or data as product).
- Japan's governance approach involving sunset provisions for therapy approvals, combined with post-market surveillance is an interesting model that has met with some success.
- Well-timed public pressure can prompt oversight.
- Society's response to a technology's off-label uses (including for enhancement) can shape its evolution as much as uptake of its intended use.
- Social structures (and future expectation of social structures) can influence uptake and vary across the globe.
- Technology can change social structures themselves (e.g., views on aging, injury).
- Access to and distribution of technology by nonlegacy players can affect use cases and uptake (e.g., the role of biohackers or the do-it-yourself community).
- Insurance coverage shapes uptake.
- For modular technologies (e.g., mRNA-LNPs), excess manufacturing capacity may act as a driver of secondary use and associated innovation.

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