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Framework for Addressing Ethical Dimensions of Emerging and Innovative Biomedical Technologies: A Synthesis of Relevant National Academies Reports (2019)

DETAILS

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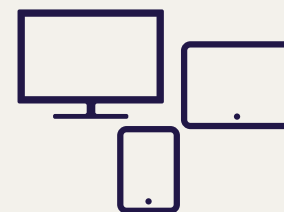
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FRAMEWORK FOR ADDRESSING ETHICAL DIMENSIONS OF EMERGING AND INNOVATIVE BIOMEDICAL TECHNOLOGIES

A SYNTHESIS OF RELEVANT NATIONAL ACADEMIES REPORTS

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INTRODUCTION

Over the past 15 years, the National Academies of Sciences, Engineering, and Medicine (the National Academies) have convened multiple committees of leading experts in the biomedical sciences and in ethics to address ethical challenges related to innovative and emerging biomedical technologies.¹ Some committees have been specifically charged with addressing ethical issues; others have addressed ethical issues as part of a broader scope of work. These committees' high-impact reports have shaped policy, practice, and discussion around core ethical issues. Some committees have developed project-specific ethical frameworks to guide their studies; others have referred to extant frameworks. Given the impact of the reports and the different ethical principles applied in each, this paper seeks to synthesize ethical principles in order to arrive at a framework for addressing some of the social and ethical challenges of emerging biomedical technologies.

This framework is different from ethics principles for researchers or philosophical discussion because it focuses on ethical challenges relevant to science policy rather than particular research projects or conceptual problems. Though there is overlap among relevant considerations, policy bodies, like the National Academies, face particular challenges with new biomedical technologies and making evidence-based recommendations that are pragmatic and address ethical concerns. This paper is the first attempt to derive a coherent framework of ethical considerations synthesized from published reports.

National Academies reports have an explicit policy focus because committees are often charged with answering policy-level questions on specific topics. Although National Academies reports frequently acknowledge existing ethics frameworks and guidance documents such as the Belmont Report or the Helsinki Declaration, the reports include adaptations or additional principles focused on practical issues and often on broad policy-oriented considerations (HHS, 2016; U.S. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1979). Other existing frameworks do not incorporate, for example, considerations from political theory or other domains that are often essential in mak-

ing policy recommendations and advising policy makers.² Because of their dual scientific and policy advisory role, National Academies projects often have a broad scope. Committees address questions ranging from what avenues of research should be pursued and how studies should be conducted or regulated to how biotechnology should be implemented within a health system. Frameworks addressing only one piece of this process or the ways that these pieces fit together will likely be incomplete for the purposes of the National Academies and similar evidence-based groups working on policy and programmatic efforts.

A well-designed framework can provide a clear and practical structure that is accessible to and useful for ethicists and non-ethicists alike and provides insights applicable to a wide range of stakeholders, including policy makers and relevant organizations and communities. An articulation of general ethical commitments or principles can be useful, but a framework to guide projects at the policy or programmatic level needs to be practically oriented in order to help identify important ethical issues and ensure that they have been effectively addressed. These goals can help to ensure that health sciences policy guidance efforts relevant to biomedical technologies are comprehensive and consistent in their approach. It can also increase efficiency by providing a starting point for discussions when addressing new policy considerations.

The framework proposed in this paper was developed by the 2018 Greenwall Foundation Fellow in Bioethics at the National Academies, Neal W. Dickert; Board on Health Sciences Policy (HSP) staff member Leah Rand; and three HSP board members who have significant committee experience and ethics expertise, R. Alta Charo (University of Wisconsin–Madison), Jeffrey Kahn (Johns Hopkins University), and Patricia A. King (Georgetown University). Based on a review of National Academies reports published over the past 15 years that address key topics in biomedical innovation and research, this framework is a derivative product and does not contain findings, conclusions, or recommendations, except those drawn from and referenced to original National Academies reports. After reviewing prior National Academies reports, individual ethics principles and considerations were identified and grouped into sets of related considerations. These considerations were then refined through iterative discussions. The resulting framework is a synthesis of principal ethical commitments

¹ Emerging and innovative biomedical technologies are defined for this paper as novel uses, modifications, or creations of biological systems or processes (Nuffield Council on Bioethics, 2019); this paper focuses specifically on the applications of these technologies in health sciences, medicine, and public health.

² “Policy makers” is used broadly to indicate groups or individuals involved in making recommendations or proposing policies relevant to biotechnologies; it is not constrained to legislators.

reflected across published reports, but it is not an exhaustive catalog. Some considerations or recommendations offered within particular reports are specific to the content focus of those reports. In addition, this framework (and the reports synthesized in its development) is limited to human applications.

Consistent with the goals of this process, it is important to acknowledge that the commitments and values within this framework do not represent an articulation or specification of a particular ethical theory. The elements of the framework represent shared commitments or values that can be justified within many theoretical orientations. The framework is designed to be of value to individuals with different theoretical commitments and, perhaps most importantly, is intended to be practically useful in structuring policy work and communicating findings to the public and to all users of evidence-based policy recommendations. It is important to recognize that an implicit commitment to rigor and carefulness undergirds the application of this framework and the treatment of ethical considerations generally, just as a commitment to independence, high-quality evidence, and rigorous peer review characterize National Academies reports more generally and ensure their independence and integrity. Those providing policy advice and making policy decisions on matters of biomedical science have a special responsibility to consider the full range of risks and implications of innovation when advising scientists, legislators, and the nation on research activities. This commitment to rigor necessitates, as much as possible, an evidence-based approach that considers both the proximate and the long-term impacts of biomedical technology or research while eschewing non-data-driven slippery-slope arguments that sometimes characterize discussions of contentious ethical issues.

While the framework is intended to guide consideration of the ethical dimensions of emerging and innovative biomedical technologies, the proposed framework is not, however, intended to restrict what any particular group should address, and each application will raise topic-specific issues. Additionally, this framework is likely to evolve. As biomedical research and innovation evolve, the ethical considerations that guide progress may change. Finally, this framework is designed to guide a process, facilitate discussion, and facilitate comparisons; it is not intended to pre-specify outcomes or recommendations.

The following section presents the eight key ethical considerations of the framework. Each consideration is defined. Examples from National Academies reports are used to demonstrate the kinds of considerations relevant to emerging and innovative biomedical technologies and to research on them. In the final section, next steps and concluding thoughts are offered regarding operationalizing and refining the ethical considerations.

FRAMEWORK FOR ADDRESSING ETHICAL DIMENSIONS OF EMERGING AND INNOVATIVE BIOMEDICAL TECHNOLOGIES

Eight core considerations or commitments make up the proposed framework for approaching ethical issues in emerging and innovative biomedical technologies (see Box 1). These considerations often overlap with each other; however, each consideration reflects a discrete and important area of emphasis. The first commitment, the promotion of societal value, clearly informs the other considerations. For this reason, it is listed first. The remaining seven are not listed in any hierarchical order.

BOX 1

Framework for Ethical Dimensions of Emerging and Innovative Biomedical Technologies

- 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 governmental and policy roles

Promote Societal Value

Biomedical innovation is principally justified by its potential to benefit society and individuals through improving health and well-being. While scientific knowledge production alone may have intrinsic value, it is ultimately the ability of biomedical research and discovery to promote health and well-being that justifies its pursuit, especially in the face of potential risks or harms (Emanuel et al., 2000). The goals of the National Academies include advancing science and its capacity to contribute to human welfare and to increase health equity. In evaluating emerging biomedical technologies, a central task of National Academies committees is thus to identify the potential for practical benefit in health and well-being, i.e., the “societal value” of a biomedical technology. Importantly, this includes not only direct health benefits but also potential positive impacts of the technology on health equity.

This consideration is listed first within this framework for two reasons. First, innovations that cannot lead to improvement in health and well-being are unlikely to be justified if they raise any significant concerns regarding risk or harm. A second, and related, reason is that understanding the potential for an innovation’s ability to produce societal value is essential for contextualizing subsequent considerations and to balancing various risks and benefits to participants or society.

Multiple reports have emphasized the importance of societal value. Reports addressing ethical implications related to embryonic stem cell research specifically described the potential of this research to address important health problems within society, and potential risks or harms are explicitly balanced against that potential to promote societal value (NRC/IOM, 2005, 2010). In a 2014 Institute of Medicine (IOM) report on human health risks and exploration spaceflight, the committee stated that National Aeronautics and Space Administration (NASA) must always consider what benefit it seeks to gain from a particular mission from the perspective of its current research agenda and the advancement of future spaceflight (IOM, 2014a). The report *Human Genome Editing: Science, Ethics, and Governance* reflects an emphasis on societal value in articulating the ethical value of “promoting well-being” and in recommending that gene-editing technologies be used only for the treatment or prevention of disease or disability for somatic genome editing and only for the treatment or prevention of serious disease or disability should it be deemed permissible to use

such technologies as heritable, germline editing (NASEM, 2017a).

In many reports, societal value considerations are explicitly invoked to balance against other kinds of considerations, as they are in the Belmont Report’s principle of beneficence (U.S. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1979). This framework separately considers societal value, negative social impact, and the advancement of patients’ and research participants’ interests. These considerations are interrelated and need to be balanced in order to avoid exploitation in the process of promoting and advancing science (Emanuel et al., 2000). This framework does not specify exactly how this balancing should be achieved and is not a checklist. Rather, it is designed to clarify distinct considerations and to make the task of balancing more explicit. This enhances its practical value (by getting relevant considerations “on the table”) and facilitates policy recommendations.

Minimize Negative Societal Impact

Just as biomedical innovation should be directed toward the production of societal value, avoiding negative societal impact is also essential. The impact of biotechnological innovations can be widespread, and a commitment to minimizing negative societal impact requires that decision makers consider the potential consequences of biomedical innovation beyond its direct impact on research participants and future patients. Potential negative societal impacts include a broad range of consequences that are particularly important in the context of making policy-oriented recommendations. While research ethics guidance traditionally addresses harms to research participants, policy makers need to consider broader questions about what harms may arise across society as a result of a program of biomedical innovation. These concerns could arise during the process of research, but they can also arise in the context of downstream implementation. Specific areas of focus in the National Academies reports addressing innovative biomedical technologies have been driven by a commitment to avoid negative societal impact, including stigma, discrimination, and increasing health inequities.

Committees routinely consider whether new biomedical technologies have the potential to increase stigma or discrimination against certain groups, and concerns about stigma have featured prominently in National Academies

reports addressing these innovative technologies. These concerns arise, for example, when technologies have the potential to reduce the prevalence of certain disabilities as a result of screening, prevention, or treatment. The report on mitochondrial replacement techniques (MRTs), *Mitochondrial Replacement Techniques: Ethical, Social, and Policy Considerations*, explicitly acknowledges concerns about eugenics and a language of “fitness” that may develop with the adoption of technologies to modify embryos (NASEM, 2016a). Such a social shift could potentially stigmatize disability and those who do not make use of new technologies, and the report argues for vigilance against shifting biologic or genetic ideals of fitness that might diminish the dignity of individuals with disabilities. In the report on human genome editing, there is a similar commitment to human dignity, rooted in the principle of respect for persons: “All people have equal moral value, regardless of their genetic qualities.” This entails a “commitment to destigmatizing disability” (NASEM, 2017a, p. 34) and takes into account negative impacts to individuals and society.

The potential for new technologies or research to increase inequities requires careful attention. Though broader distributive justice issues in health care are beyond the scope of work for many policy makers or programs, the identification of potential inequities and how to address them indicates a commitment to minimizing societal impacts. The report on MRTs specifically addresses the potential for the introduction of MRTs to increase health inequities because MRTs will likely be highly expensive and initially available only to relatively well-off individuals with health insurance that covers them (NASEM, 2016a). Difficulties in access may exacerbate health and social inequities because those with means may be able to have children without a devastating disease, while individuals who are less well-off or too distant from sites offering the technology might either have to forgo having children or risk the child having a serious illness. The report explicitly advises that inequitable access that is a function of the current health care system should not derail advancement but also advises that the implementation of this technology must include efforts to identify individuals who can benefit most. This example illustrates not only an attention to issues of potential negative social impact—the societal harms caused by limited access—but also a need to consider these impacts against potential societal benefits—the promotion of societal value. Addressing disparities and inequities is complex. It is often the case that access to new technologies or therapies is initially limited by financial or other resource considerations that, over time, may attenuate, allowing broad and affordable

access to important benefits. In this respect, disparities are not all the same; some are more problematic than others. The case of MRTs highlights the importance of paying special attention to situations where inequitable access can produce a demonstrable negative impact on those who lack access.

There are additional forms of potential societal impacts of research on individuals and communities. Research in a particular area may affect clinical care, for instance, and it is also important to consider the effects of research on non-participants. This set of issues was addressed in the report *Opportunities for Organ Donor Intervention Research: Saving Lives by Improving the Quality and Quantity of Organs for Transplantation* (NASEM, 2017b). A fair allocation system for organs is essential and should not be jeopardized by clinical research. Plans for organ donation research, for example, must address the risk of alienating the public and reducing donor organ availability. Society can be made worse by the presence of some disparities, so attention to the potential for negative societal impact is important when making recommendations about new technologies.

Protect the Interests of Research Participants

The goal of protecting the interests of research participants focuses specifically on clinical research, an essential stage in the development of innovative biomedical technologies. It is rooted in long-held positions in bioethics about the importance of avoiding harm to and exploitation of research participants. In considering novel biomedical technologies, it is important to recognize the moral constraints of using individuals (typically humans, although similar considerations are relevant for animals) as research participants (IOM, 2003).³ The primary goal of the research process is the generation of knowledge, and a principal ethical goal is to avoid compromising individuals’ interests or well-being in that process. When evaluating new technologies and research, it is important to take into account the rights and interests of participants and to identify and account for issues that affect their welfare.

Ethical commitments to protect research participants’ interests are the focus of multiple guidelines and regulations, ranging from the Nuremberg Code to the Belmont

³The scope of this paper is limited to human research and the effects of biomedical technologies. The National Academies have addressed the protection of animals in research in several reports, including IOM, 2011; NAS/IOM, 1991; NRC, 1998, 2011.

Report and the Federal Common Rule (45 C.F.R. Part 46 HHS, 2016; U.S. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1979). Broadly, there are two kinds of protections that are critical to consider. One form of protection focuses on individual welfare. The potential risks of research participation must be taken seriously and weighed against both potential benefits to individual participants and potential societal value. A second form of protection that follows from this commitment is the focus on rights and other interests that participants have. The reports of the National Academies frequently call attention to the importance of informed consent and other measures to ensure respect for persons. While attention to these considerations may advance participants' welfare interests, a primary motivation is also to ensure the protection of rights and interests that extend beyond participants' health or welfare (e.g., protection of privacy interests). This commitment can be found in reports recommending consent for human embryonic stem cell research, which have recognized the additional moral significance that some people attach to embryos (NRC/IOM, 2005, 2010).

Steps that researchers should take to protect research participants and their interests are outlined in the 2003 IOM report *Responsible Research: A Systems Approach to Protecting Research Participants*, which recommends guidelines for human-subjects research (IOM, 2003). The recommendations include the implementation of a systems approach designed to protect autonomous and informed consent, accountability, and adequate resources for sustaining the protection of participants. These requirements were particularized to children in *Ethical Conduct of Clinical Research Involving Children* (IOM, 2004). Additional protections that are generally relevant and are raised in the context of novel biomedical technologies include privacy protections (NRC/IOM, 2010) and the consideration of returning research results as a part of a commitment to demonstrating respect for participants, ensuring transparency, and developing trust between researchers and participants (NASEM, 2018).

Many of the protections essential to conducting human-subject research in general are applicable to biomedical technologies, but these technologies introduce novel challenges as well. Genome editing, for example, challenges definitions of who counts as a research participant. Germline genetic interventions have implications for future persons, and their interests need to be explicitly accounted for and protected. Many studies of emerging and innovative biomedical technologies may also affect close associates of research participants such

as spouses or family members. These considerations are distinct from issues related to bystander effects or societal impact (addressed in a prior section on avoiding negative societal impact) because they directly affect individuals connected to the research.

It is important to recognize that individuals' participation in research is often driven not only by a desire to assist in research but also by clinical goals, and participants frequently occupy the roles of patient and research participant simultaneously. As research participants, they are involved in knowledge generation, and it is ethically necessary to protect their interests in the design and conduct of studies. As patients, individuals' involvement may be primarily oriented toward clinical benefit. In many cases, these interests may align, but they can exist in tension. Protecting research participants' interests is thus a commitment that has distinct features from the advancement of patients' interests.

Advance the Interests of Patients

In contrast to the protection of research participants' interests, a commitment to advancing patients' interests focuses on the clinical application of innovative biomedical technologies, whether in the health system context or otherwise. The reason for the clinical use of any biomedical technology is presumably for the benefit of individuals with the relevant conditions or, in the case of preventive therapies, who may be at risk for developing those conditions. The aim of this consideration is to advance those benefits and patients' interests while minimizing risk. This is different from protecting research participants from the risk of a process aimed at knowledge development. However, as acknowledged previously, research involving new biomedical technologies often involves patients, and both sets of considerations apply.

The scope of the commitment to advancing patients' interests is broad and involves important policy-level considerations. For example, this commitment requires careful consideration of justice and fairness issues related to access. These considerations overlap with, but may be distinct from, the concerns discussed earlier regarding health inequalities or the exacerbation of disparities. Careful consideration of patients' interests should also substantially inform and drive decisions regarding the regulation of novel biomedical technology as it emerges into clinical use.

The process of respecting and advancing patients' interests becomes more complicated when dealing with innovative reproductive technologies. Germline gene editing and mitochondrial replacement techniques both may make it possible to have genetically related children without a heritable genetic disease. Both types of therapies, however, may also pose risks to the child through unknown effects of genome editing. For this reason, two National Academies reports recommend the research and eventual use of these new techniques for only the most severe and debilitating of conditions (NASEM, 2016a, 2017a).

Protective considerations can, as discussed, exist in tension with the advancement of individual patients' interests. Additionally, substantial tension can exist between the advancement of research goals (including the production of rigorous data) and the advancement of individual patients' interests. Many new biomedical technologies, especially those involving genome editing, are likely to remain experimental for a considerable time, so gaining access to clinical benefits may require involvement in research (NRC, 2002; NASEM, 2016a, 2017a).⁴ Patients or patient groups, however, may have a strong desire for clinical access to experimental interventions available only in the context of clinical trials. Tensions about access to innovative therapy are clearly illustrated by the recent "Right to Try" movement and the resultant federal legislation (Public Law 115-176). It is important to consider how a new biomedical technology may advance patients' interests without losing track of its implications for research participants or its potential for negative societal impact. The latter set of concerns is particularly central to debates regarding genome editing, as reflected in the National Academies report on this issue (NASEM, 2017a).

Maximize Scientific Rigor and Data Quality

The value of scientific research is contingent on its effective design and execution. A central ethical commitment is thus adherence to high standards of research conduct and scientific practice. Flawed research designs can harm research participants, waste resources, fail to generate valuable data for patients and society, and compromise public support for and trust in the research enterprise. Well-designed research that is poorly executed poses similar threats. Potential threats to data quality in the process of studying a new biotechnology thus deserve strong consideration

⁴ This is not a new consideration; the 1980s, for example, saw a push for access to AIDS treatments in development that were only available to a limited number of research participants (IOM, 2007).

when making recommendations on future biomedical research.

Several specific considerations related to scientific rigor and data quality have been made in previous National Academies reports. Validity is an important principle guiding research—for research to be beneficial and productive, it must be valid and should produce findings that are accurate and can be applied in real clinical settings (NASEM, 2017b). New technologies involving biological specimens also require extra care related to the appropriate management of samples. These responsibilities take on special significance in the context of embryonic stem cell research, for example (NRC/IOM, 2005).

An additional consideration related to maximizing rigor and data quality that has been highlighted in prior reports is the need for increased data sharing. The report *Sharing Clinical Trial Data: Maximizing Benefits, Minimizing Risk* highlights the benefits of working toward increased data sharing; among these is the ability to conduct further analyses that may generate additional findings, reframe conclusions, and protect patients (IOM, 2015). The report identifies important challenges, ranging from individual privacy risks to the protection of intellectual property, and recommends oversight from an independent review panel and a transparent process for granting access. In a similar vein, the report on clinical gene transfer protocols recommends that advisory committees overseeing research protocols be used to integrate the capacity to "surveil, aggregate, and analyze adverse events across related trials of emerging technologies" (IOM, 2014b, p. 7). Maximizing rigor and data quality thus increases the value of research and can help to minimize risks to patients and participants, linking this particular consideration to other considerations involving societal value and the protection of research participants' interests. Finally, the potential for increased data sharing further accentuates the need for data quality and methodological rigor.

Engage Relevant Communities

National Academies reports have frequently called for a commitment to community engagement in multiple forms. New technologies in health and medicine raise socially challenging questions and genuine ethical dilemmas. Democratic engagement with the public provides input and a range of perspectives on how best to meet these social and ethical challenges. More generally, because innovations in biomedical technology have potentially

important impacts within society, the process of development, research, and implementation should be influenced by the public these innovations are intended to serve. Consideration of whether and what kind of community engagement is most appropriate for the particular technology will be important.

Multiple reasons for and forms of community engagement have been described in National Academies reports related to innovative biomedical technologies. The report on human genome editing specifically recommended that public input precede any clinical trials in germline gene editing (NASEM, 2017a). The report notes that public engagement is bi-directional; it can serve as a means for researchers to inform the public as well as for researchers to receive input and perspective from the public. In addition, engaging the public in deliberating about policy decisions may help to legitimize approaches to a morally challenging decision. Such full-spectrum engagement is emphasized as being particularly important prior to potential clinical use of germline editing given the heritable nature of the genetic changes and substantial heterogeneity among the public regarding key moral questions in this domain (NASEM, 2017a).

Community engagement has also been recognized as serving the important functions of building trust within a relevant community, demonstrating trustworthiness to a community, and fostering public engagement with science and research generally. An example of engagement for the purpose of building public trust in the research community is the recommendation from the report on clinical gene transfer protocols that the National Institutes of Health (NIH) establish a public forum for review and discussion that would foster public awareness of emerging science and provide an opportunity to address and discuss public concerns about emerging and innovative biomedical technologies (IOM, 2014b). The 2018 report *Returning Individual Research Results to Participants: Guidance for a New Research Paradigm* emphasized that returning results to research participants is a means to broaden engagement with research participants. Greater engagement with participants and participant groups has been recognized as having potential additional benefits related to increasing the representation of traditionally underrepresented groups in research (NASEM, 2018).

The National Academies reports on innovative biomedical technologies have emphasized international collaboration and engagement in an era of growing connectedness. These reports thus reflect a broad notion of community engagement that extends beyond the affected public or

patient population and needs to be specified in the context of a particular biotechnology. The report on MRTs, for example, highlights the value of transnational partnership among countries and researchers as a guiding principle for MRT research and application (NASEM, 2016a). The report calls for the United States to pool data with other countries in order to assess the benefits and risks of MRTs. Similarly, the report on human genome editing recommends transnational cooperation as a principle governing gene-editing research and clinical application. Responsibilities that would flow from adherence to this principle include the coordination of regulatory standards where possible while respecting national contexts and policies. The principle also emphasizes an important role for collaboration and data sharing in order to responsibly advance genome editing research, application, and oversight (NASEM, 2017a). This commitment to broad and context-sensitive understanding of community engagement is reflected in National Academies reports related to non-human uses of biotechnology (e.g., gene drives) as well (NASEM, 2016c).

Ensure Oversight and Accountability

The values of accountability and oversight are essential throughout the process of developing, studying, and implementing novel biomedical technologies. In a sense, processes that ensure both accountability and oversight are the “tools” through which many of the other ethics considerations described within this framework are realized. Along with broad engagement, processes designed to ensure accountability and proper oversight can help to demonstrate trustworthiness and provide transparency, both of which are essential when addressing social questions and ethical concerns raised by emerging and innovative technologies. This involves exploring the existing accountability mechanisms and determining whether special oversight of a new biomedical technology or research is required.

In addition to the legal requirements for human-subjects research, further mechanisms of ensuring accountability and oversight have been recommended in previous reports. Some reports, such as the one on the oversight and review of clinical gene transfer protocols, have focused almost exclusively on assessing the adequacy of oversight mechanisms (IOM, 2014b). Just as in other domains, future work addressing novel technologies will need to adapt to a changing landscape with increasing access to large amounts of data. National Academies reports outside the scope of novel biomedical technolo-

gies can be highly informative. The 2007 IOM report *Ethical Considerations for Research Involving Prisoners*, for example, focuses heavily on oversight mechanisms when enrolling a highly vulnerable population (IOM, 2007); these concerns are germane to work involving novel therapies such as germline gene editing and mitochondrial replacement therapy, which also involve vulnerable individuals.

Recognize Appropriate Governmental and Policy Roles

As described in the introduction to this framework, a central function of policy-oriented bodies, such as National Academies committees, is to make policy recommendations, often to governmental regulatory agencies. This role is distinct from the role of individual researchers and requires careful consideration of what the role of governmental action and policy should be in regulating research and the applications of biomedical technologies. Recommendations aimed specifically at the U.S. government best take account of governmental roles when they reflect both the division of authority between federal and state governments and between government and individuals; those directed toward the international community reflect an awareness of the diversity of forms of government across the globe and the limits of international law. Policy-level approaches to ethical challenges need to be conscious of individual liberties, the role of religious or conscience-based concerns, and the reasonable reach of the state.

Scientific developments involving human embryos and embryonic stem cells, which have been the focus of several National Academies reports, present important challenges because of differing moral views in American society concerning the ethical nature of these technologies. The report *Guidelines for Human Embryonic Stem Cell Research* explicitly recognized this pluralism of views regarding the moral status of embryos and reached the conclusion that the appropriate response is government oversight and regulation rather than a total ban on the research (NRC/IOM, 2005). The report on human genome editing recommends government oversight and regulation of genome editing in several contexts, including research using human cells and tissues and development of non-heritable (somatic) genome editing applications. It also emphasizes a need for a stringent oversight system and further public engagement prior to initiating any clinical trials and applications of heritable, germline gene editing (NASEM, 2017a). The report on MRTs similarly

recommends that the U.S. Food and Drug Administration should regulate MRTs to ensure that they are used only in approved settings and that public consultation should take place prior to any expansion of their use (NASEM, 2016a). This recommendation for government regulation curtails individual reproductive liberty by placing MRTs under governmental oversight, but in recommending that MRT research go forward, it also respects the value that many individuals place on having genetically related children. In each of these cases, committees have had to consider explicitly the role of regulation and governmental action in a context of substantial public moral disagreement. Recommendations to the government are pragmatic when they fit within its regulatory rules and limits, which are constitutionally prescribed and often driven by underlying ethical principles.

Prior work also illustrates the way in which proper governmental roles evolve. As research advances, knowledge grows, and social views on the technologies change, the role of regulatory agencies may also change. In the report *Oversight and Review of Clinical Gene Transfer Protocols: Assessing the Role of the Recombinant DNA Advisory Committee*, the authoring committee determined that the Recombinant DNA Advisory Committees (RAC), which oversees gene transfer research at NIH, could limit the public review of research protocols to those that meet a few specific criteria (IOM, 2014b). The original need for a public review of research protocols arose because gene transfer research was a new technology in clinical research that raised substantial public concerns and stoked the public imagination. As the science developed, the review and regulatory process became more focused. This example demonstrates how oversight and regulation change in response to experience and, in particular, in response to changing public views about the acceptability of specific forms of research.

Groups advising on policy decisions have a responsibility to consider their recommendations in the context of real-world policy settings while remaining forward looking. This is reflected in an emphasis on the responsibility to perform evidence-based assessments of future impact when possible, while at the same time confronting the real-world issues that make up the context in which novel biomedical technologies will emerge. For example, policy makers may address barriers to accessing a new treatment as part of their recommendations. However, at the same time, they need to be cognizant of the regulations and inherent limitations of the health care system into which a new treatment modality will be introduced.

BOX 2

National Academies Reports Discussed in the Framework

- *Returning Individual Research Results to Participants: Guidance for a New Research Paradigm* (2018)
- *Human Genome Editing: Science, Ethics, and Governance* (2017)
- *Opportunities for Organ Donor Intervention Research: Saving Lives by Improving the Quality and Quantity of Organs for Transplantation* (2017)
- *Mitochondrial Replacement Techniques: Ethical, Social, and Policy Considerations* (2016)
- *Gene Drives on the Horizon: Advancing Science, Navigating Uncertainty, and Aligning Research with Public Values* (2016)
- *Sharing Clinical Trial Data: Maximizing Benefits, Minimizing Risk* (2015)
- *Health Standards for Long Duration and Exploration Spaceflight: Ethics Principles, Responsibilities, and Decision Framework* (2014)
- *Oversight and Review of Clinical Gene Transfer Protocols: Assessing the Role of the Recombinant DNA Advisory Committee* (2014)
- *Final Report of the National Academies' Human Embryonic Stem Cell Research Advisory Committee and 2010 Amendments to the National Academies' Guidelines for Human Embryonic Stem Cell Research* (2010)
- *Ethical Considerations for Research Involving Prisoners* (2007)
- *Guidelines for Human Embryonic Stem Cell Research* (2005)
- *Ethical Conduct of Clinical Research Involving Children* (2004)
- *Responsible Research: A Systems Approach to Protecting Research Participants* (2003)
- *Scientific and Medical Aspects of Human Reproductive Cloning* (2002)

DISCUSSION OF NEXT STEPS

This framework draws from multiple National Academies reports and offers a set of ethics considerations that are broadly applicable in evaluating emerging and innovative biomedical technologies. The framework is not intended to be constraining but is intended to be practical and action guiding in three key respects.

First, it provides a structure for systematically evaluating the ethical implications of emerging and innovative biomedical technologies. In this way, it can help to identify and clarify what is at stake in addressing a particular set of issues and to illustrate competing considerations. It does not, however, resolve difficult conflicts between competing considerations. For example, the sections on advancing patient interests and protecting research participants explicitly draw out some of the ways in which a person's position as both a participant and as a patient may suggest different interests. Similarly, individual patient interests may need to be considered against the potential for negative societal impacts. The presence of these conflicts does not undermine the framework, and the framework is not an ethical checklist. Rather, the framework functions in many cases to clarify and characterize conflicts. Policy efforts for emerging and innovative biomedical technologies often require “the balancing of two critical values—the protection of human participants in research and the advancement of medical science to benefit society” (IOM, 2014b, p. 17). When considering policy recommendations for emerging and innovative biomedical technologies, policy makers and others working in this area can explain their rationale for balancing the ethical considerations in the manner they did. The bodies receiving the recommendations, often federal agencies, then have the opportunity to weigh similar evidence and recommendations when deciding how and whether to implement a report's recommendations.

Second, and closely related, the framework of ethical considerations serves to identify a core set of values that characterize the National Academies' work in the domain of emerging biomedical technologies. In this respect, it is hoped that this framework will help to facilitate comparisons across efforts to address ethical dimensions of science policy for emerging biotechnologies and, where appropriate, lend a measure of consistency in approach or language across these efforts.

Third, this framework is aimed at promoting efficiency by minimizing the work needed to identify and articulate

general ethical principles or guidance at the outset of the policy recommendation process. This work can thus be focused on unique areas of concern raised by the biotechnology issues being studied.

While these properties are undoubtedly valuable, this framework is limited in several ways. Specifically, it is novel, has boundaries, and is focused on emerging biomedical technologies as applied to improving human health and well-being. There is more work to be done. It will be important to understand whether this framework could be helpful more broadly beyond the domain of emerging biomedical technology. The values set forth within the framework are not highly specific and could be the starting point for an articulation of values or ethics considerations across a broad range of issues in biomedicine. For example, the use of big datasets for research and what that means for individuals' privacy and status as research participants could be examined through this framework. Similarly, it may be of use in or adapted to the evaluation of non-human and non-biomedical applications of biotechnology, such as the genetic engineering of crops (NASEM, 2016b), or to evaluating innovations outside of biotechnology with potential implications for human health such as artificial intelligence; however, it has explicitly been developed with an emphasis on the biomedical applications of biotechnology.

There is also more work to be done to explore both the underlying justifications and further specification of each of these considerations. The framework focuses on what may be most appropriately labeled middle-level considerations. They are middle level in the sense that they are not general theoretical or abstract ethical principles and they are not highly specified requirements. Rather, these considerations reflect widely shared values that have been embraced or reflected in the work of the National Academies that may help to structure future deliberations and identify important ethical challenges. In addition, they can help to provide consistency in approaches across projects and facilitate the communication of efforts addressing similar or related topics. Further work on justifying the nature of each consideration from various philosophical or theoretical perspectives will be of value in understanding both the strength of each commitment and the more specific implications in real-world contexts. This is critical, especially for understanding the implications of these considerations in the context of new situations and those characterized by conflicting considerations.

Finally, the framework is expected to evolve. New innovations may disrupt current thinking about the ethical dimensions of innovation and research and may demonstrate the need for new values or revisions to the current framework. Similarly, the application of this framework to the range of topics addressed by National Academies committees and their like will surely identify gaps and areas for further development. This is desirable and important. One of the key virtues of a framework such as this is its utility in structuring ongoing discussions about the ethical dimensions of emerging biomedical technologies. For committee members, policy makers, and advisers, this framework can provide a starting point for determining if an innovative biomedical technology raises new ethical concerns and also for deliberating about the best ways to identify and act on the ethical commitments that should undergird biomedical research.

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