NOVEL AND EXCEPTIONAL TECHNOLOGY AND RESEARCH ADVISORY COMMITTEE

Minutes of Meeting

December 5-6, 2019

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

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NATIONAL INSTITUTES OF HEALTH
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MEMBERS
Richard Whitley, M.D. (Chair)
Zach N. Adelman, Ph.D.
Lorraine M. Albritton, Ph.D.
Kathleen Boris-Lawrie, Ph.D.
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Matthew Porteus, M.D., Ph.D.

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Cinnamon Bloss, Ph.D.
Kafui Dzirasa, M.D., Ph.D.
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Kenneth Oye, Ph.D.
Margaret F. Riley, J.D.
Kim M. Thiboldeaux
Leigh Turner, Ph.D.

NExTRAC is a federal advisory committee that provides recommendations to the NIH Director and serves as a public forum for the discussion of the scientific, safety, and ethical issues associated with emerging biotechnologies. NExTRAC proceedings, reports, and links to meeting videocasts are posted on the OSP website to enhance their accessibility to the scientific and lay public.

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DAY 1

CALL TO ORDER

Richard Whitley, M.D., NExTRAC Chair

Dr. Whitley called the meeting to order at 10:59 a.m. He announced that the meeting was being videocast and recorded. NIH staff will post the slides of the presenters to the NExTRAC website.

USHERING IN A NEW ERA OF RESPONSIBLE INNOVATION

Francis S. Collins, M.D., Ph.D., NIH Director

Dr. F. Collins welcomed everyone in the room and those participating via videocast to the inaugural meeting of NExTRAC. The establishment of NExTRAC built upon the prior work of the NIH Recombinant DNA Advisory Committee (RAC). He expressed his gratitude for the opportunity to convene this distinguished group to advise NIH.. The new era of biotechnology and biomedical research is breathtaking in its sweep and potential consequences, which demand a high level of thinking. The pace of progress is accelerating and is gratifying in terms of its promise, but the pace also raises complicated questions about oversight of these efforts. Before issuing the charge to this group at the end of the meeting, Dr. F. Collins and other NIH leaders wanted to learn what NExTRAC members think about relevant issues.

Biotechnology offers great promise, bringing hope and help for those who are seeking answers. Advances include the Brain Research through Advancing Innovative Neurotechnologies® (BRAIN) Initiative, CRISPR-Cas9 gene editing,[1] gene drives, and artificial intelligence (AI) applications, among others. Nevertheless, some activities cause concern to NIH and the public. One example is the unfortunate experiment carried out in China involving heritable genome editing in humans. People are also worried about some potential products of organoid research.

Such concerns are hardly new. In the 1980s, worries focused on genetic engineering; in the 1990s, on cloning; and in the 2000s, on the Human Genome Project. Now concerns are emerging about genome editing. Media reports have in the past and are still today raising the question of whether recombinant DNA work amounts to "playing God."

Dr. F. Collins posed a series of questions reflecting overarching considerations for emerging biotechnologies:

- How can we anticipate emerging biotechnologies that will create policy, safety, ethical, or security challenges in a preperatory/anticipatory mode?
- How can we develop a flexible or dynamic oversight framework that evolves with biotechnology?
- When do we know that an emerging biotechnology has emerged?

- How do we keep the focus on the applications of the biotechnology rather than on just the science behind the biotechnology?

Human Genome Editing

Dr. F. Collins reviewed the history of approaches for addressing emerging genetic biotechnologies. The 1975 Asilomar Conference provided an opportunity to discuss the potential risks and safety concerns of recombinant DNA research. That meeting eventually led to the formation of the RAC and the development of the *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules* (*NIH Guidelines*). The RAC focused mainly on recombinant DNA, but its purview expanded to human gene therapy. In 1989, the first human gene transfer protocol was reviewed by the RAC and approved by the NIH director. Since 1997, the NIH director no longer had to approve protocols since since sufficient regulatory oversight existed with the Food and Drug Administration (FDA);. For the next 20 years the RAC's role continued as a venue for in-depth review in a public setting. Dr. F. Collins said that in 2016, RAC review was limited to novel and original protocols, per the recommendation of the National Academy of Medicine (at the time, the Institute of Medicine). In 2019, efforts have focused on streamlining the oversight framework for emerging technologies, leading to the formation of NExTRAC.

Dr. F. Collins highlighted advances in human gene editing. NIH supports many research initiatives involving somatic cell gene editing, including the Somatic Gene Editng Intiative and Cure Sickle Cell Disease. NIH and the Bill & Melinda Gates Foundation are collaborating on an initiative to bring somatic-cell gene therapy for HIV infection and sickle cell disease to Africa.

Different applications have different levels of risk. Heritable genome editing (in germline cells) poses greater concern than somatic cell editing because the genetic changes are transmitted to subsequent generations. NIH does not fund any use of gene editing technology in human embryos. In fact, Congress has prohibited FDA reviews of this type of research. Perhaps there are some rare medical needs that only heritable gene editing could meet, but societal, ethical, and moral issues would need to be addressed, including consent, justice, and equity, as well as philosophical and theological concerns. Coming up with global governance and oversight would be a major challenge. However, the World Health Organization (WHO) and the US National Academy of Sciences together with the UK Royal Society have panels debating some of these issues. Whether NExTRAC will have a role in this space remains to be seen- other applications involving gene editing, such as gene drives, are likely to require the committee's attention.

Neurotechnologies
Emerging neurotechnologies are another area of enormous potential and concern. Dr. F. Collins updated the group on the BRAIN Initiative. The 2014 report, *BRAIN 2025: A Scientific Vision,* laid out a 10-year plan for the initiative. In 2019, a group of experts evaluated progress and scoped out a plan for future research. Progress at the midway point has exceeded projections.

BRAIN investigators are conducting *in vivo* neuroscience research with research participants undergoing neurosurgery for clinical indications. This research is providing extraordinary insight into how the human brain works, as exemplified by a recent publication highlighting how brain signals can be translated into synthesized, recognizable speech.

The BRAIN Initiative's Neuroethics Working Group is identifying and navigating neuroethical challenges, developing neuroethical research questions for research inquiry, and convening workshops. The Advisory Committee to the Director (ACD) has put forward a proposed neuroethics roadmap in a report *The BRAIN Initiative and Neuroethics: Enabling and Enhancing Neuroscience Advances for Society*.

Evolution of the NExTRAC
Dr. F. Collins explained how the NExTRAC is the next phase of the RAC. For more than 40 years, the RAC has addressed issues associated with basic scientific advances involving recombinant DNA in the 1970s and evolved to cover human gene therapy in the 1990s. In 2019, the focus is on research involving emerging biotechnologies. The *NIH Guidelines*, as amended in 2019, eliminated the RAC review, protocol registration, and reporting requirements associated with gene therapy research. The RAC, renamed as the NExTRAC, will now align more closely with its original focus: serving as a public forum for discussing the most challenging questions that arise from emerging biotechnology research.

The NExTRAC will be a public forum for transparent discourse on challenging issues, a source of advice to the NIH director, and a resource for the scientific community and the public. Dr. F. Collins said that the NExTRAC will focus on the scientific, safety, and ethical issues associated with emerging biotechnologies, such as gene editing, gene drives, synthetic biology, and neurotechnology and perhaps on cutting-edge clinical applications.

Dr. F. Collins spoke about encouraging and nurturing technologies to benefit humankind, and he said that technology should not eclipse our humanity. He emphasized the importance of anticipating the challenges of emerging technologies.

Discussion
Dr. Leshner inquired about the purviews of other advisory groups and the potential for overlap with the NExTRAC. Dr. F. Collins said the plan is to avoid duplicating effort, but different groups bring different perspectives. The NExTRAC has broad diversity and expertise and is positioned to capture a wider view than other groups that focus on

specific aspects of biotechnologies. The NExTRAC will be unique in its anticipatory view; most other groups focus on acute issues regarding biotechnologies that are past the emerging phase. The NExTRAC will look into the urgent ethical challenges of the day.

INTRODUCTION OF COMMITTEE MEMBERS AND CONFLICT-OF-INTEREST DISCLOSURES

Richard Whitley, M.D.

The members of the NExTRAC introduced themselves.

Dr. Jessica Tucker, the NExTRAC Executive Secretary, reminded NExTRAC members of the rules of conduct that apply to them as Special Government Employees, read into the record the conflict-of-interest statement, and indicate that related questions could be addressed to the Committee Management Office.

SESSION I: PATHWAYS FOR RESPONSIBLE INNOVATION IN EMERGING BIOTECHNOLOGY

Panel Discussion

Moderator: Carrie D. Wolinetz, Ph.D.
Panel Members: Gary Marchant, J.D., Ph.D., and Larisa Rudenko, Ph.D., DABT

Dr. Wolinetz said this panel session was intended to be a broad, cross-cutting discussion about possible oversight and governance mechanisms for emerging biotechnologies. She posed a series of questions for the panel members to discuss.

- What are the current key themes and principles for governance and oversight (e.g., risk versus benefit) for emerging technologies? How far ahead of the science does NExTRAC need to be?

Dr. Marchant said that the current system for governance and oversight has been cobbled together by adapting other regulations and applying them to biotechnology. Cracks in the governance system are starting to appear. Major issues for the public lie within the ethical and social domains, but these areas are not within the purview of regulators. Another challenge is pacing. Governance structures would need to adapt nimbly, given the accelerating pace of biotechnology development. Dr. Marchant also compared various applications of emerging technologies; for example, biotechnology could be used for enhancement, such as improving test performance, rather than disease treatment. Such enhancement applications pose challenges for regulation.

Another challenge is the international setting: How could governance and oversight be extended to prevent situations like that of the Chinese scientist who performed heritable genome editing in humans? These challenges are already apparent and will only grow.

- What lessons have we learned from recombinant DNA technology in terms of oversight and public engagement?

Dr. Rudenko noted that the aim of this meeting is to talk about emerging technologies, but the US regulates products, not processes. Dr. Rudenko also pointed out that, during her tenure at the FDA, public comments were often based on values, which the FDA cannot even consider. In the absence of other information, safety often ends up being a surrogate for values-based concerns. At the intersection of science and society, there may be active and passive opportunities for oversight and "soft" governance. Regarding the pacing problem, Dr. Rudenko said that the government is slow to develop policies; however, nearly all U.S. regulatory and funding agencies have components in the experimental phase. The perception is that the future is an inchoate mist. How one views the risks associated with emerging technologies largely depends on the potential benefits and where one sits on the spectrum of risk aversion versus risk tolerance.

- What is the role of public forums for discussing emerging technologies?

Dr. Rudenko observed that the Office of Technology Assessment (OTA)[2] had provided a good forum for discussing technologies in a transparent way, but OTA no longer exists. Congress is discussing the possibility of resurrecting OTA. The White House Office of Science and Technology Policy may serve as a broker of information with some transparency. With transparency comes the responsibility to come to the table in good faith. Dr. Marchant said that the National Academies of Science and Government Accountability Office have taken on much of the work of the former OTA, but it operates largely behind closed doors. In contrast, the NExTRAC is an open forum. Although transparency is sometimes ugly and involves arguments, it has major process value. Insofar as opportunities for public input, most people would not be willing to travel to NIH. They suggested creating more opportunities in different parts of the country to allow more people to participate in discussions.

- What are some potential cross-cutting issues that could be built into an adaptive oversight framework that could take into account the safety, values, ethics, and scientific issues that the NExTRAC could consider?

Dr. Rudenko said that safety, values, and scientific considerations are multidimensional issues. In thinking about opportunities to enhance discussions and governance, Genome Canada looks at traditional ecological knowledge with respect to the grants itawards ; there may be a lesson to apply with regard to grants funding. Dr. Marchant said that there are concerns about technologies in general. He recommended learning more about what has happened in the context of the BRAIN Initiative, nanotechnology, and AI. These are different novel technologies, but the same underlying themes keep coming up.

Dr. Rudenko contrasted technologies and their applications. For example, the same basic process could apply to early stages of technologies for regenerative medicine and for cultured meat, representing very different applications of similar technologies. Cultured meat would likely be regulated by the FDA's Center for Food Safety and Applied Nutrition, but the regenerative

[2] OTA was an office of the United States Congress from 1972 to 1995. OTA's purpose was to provide Congressional members and committees with objectives and authoritative analysis of the complex scientific and technical issues of the late 20th century ("Office of Technology Assessment," Wikipedia).

medicine application might also include AI, 3D printing, and machine learning, making the regulatory picture more complex.

Dr. Marchant discussed some challenges associated with premature access to treatments, but the public gets impatient waiting for years of clinical trials to be completed before a new treatment comes to market. For example, the "right to try" proposition was supported by 82% of the public, even though mechanisms were already in place to provide access to experimental treatments. The do-it-yourself (DIY) approach evolved due to impatience with governance systems. How do we communicate that many people are paying large sums for purported treatments that will not help and might hurt them?

Dr. Rudenko suggested that the FDA and the U.S. Department of Agriculture (USDA) could work together to allow service and companion animals to be part of research studies to evaluate therapeutic effects of animals, treatments for animals, and the animals as models of human disease. However, NIH keeps control over any animals used in research and does not release them from containment unless another agency takes over. People do not want their pets to be kept in cages in a laboratory; they want their pets back at home. Dr. Rudenko thought that addressing this issue should be low-hanging fruit that could be addressed by the FDA and the USDA

- Public trust is important for scientific progress. How can we maintain trust in oversight and governance systems and applications of biotechnologies?

Dr. Marchant spoke of the importance of public engagement. People appreciate open proceedings, transparent operations, and opportunities to present their views and values. The NExTRAC's open process could help reduce frustration and concern. Dr. Marchant recommended that the NExTRAC facilitate more online engagement to help counter false information.

Dr. Rudenko agreed with Dr. Marchant about the importance of democratizing science and holding face-to-face and virtual meetings to encourage public engagement. The NExTRAC could help frame discussions to attenuate some of the social risks associated with emerging biotechnologies.

- When new fields of science are emerging that might present concerns, when should we introduce governance, oversight, policies, and guidelines to address the risks and concerns without impeding the science?

Dr. Rudenko cautioned against assuming that more knowledge will mitigate social concerns about emerging biotechnologies. Social and values-based concerns are not the results of a knowledge deficit. She recommended avoiding being coercive or giving the appearance of coercion. People tend to view technologies as being on a spectrum that culminates in transformative and truly disruptive developments. For example, many people are concerned about genetically modified organisms, but how does moving a few genes or nucleotides via gene-editing technology differ from selective breeding? However, we have to be able to deal with emerging technologies being perceived as disruptive steps as well as part of a continuum.

Dr. Marchant said that public engagement is challenging. For example, the Nanotechnology Cafes were supposed to engage the general public, but the events attracted only university students. People are rationally ignorant because they are busy. He recommended thinking about where people interact with technology and being proactive. Insofar as governance, policies, and so forth, Dr. Marchant advised against putting hard and fast rules in place while things are evolving and recommended instead thinking about codes of conduct and best practices, which can apply broadly—even internationally—and change rapidly. The regulatory law system is hard to adapt.

General Discussion

Mildred Cho, Ph.D., encouraged the inclusion of stakeholder groups that are responsible: individual scientists, technology developers, as well as their institutions in discussions about oversight and governance. Although these topics seem external to the scientific community, its involvement is even more critical with emerging technologies because of the need to focus issues early, before or during the design stage.

Pilar N. Ossorio, Ph.D., J.D., commented on the timeframe issue, noting that the FDA requires developers to produce evidence of safety and efficacy. People think that treatments are being withheld from them, but a product is not a treatment until safety and efficacy evidence is accrued. She recommended pushing back against the narrative about government being slow to allow new technologies to come to market because considering evidence, especially of efficacy, matters. Dr. Rudenko agreed about the importance of disseminating information about levels of evidence, guidelines, and policies to show that the government is prepared.

Dr. Rudenko recommended using a recursive process to establish ground rules that could be adapted. Dr. Marchant supported the idea of having a dynamic evidence system.

Ms. Thiboldeaux advocated keeping public engagement front and center, and she spoke of the need for better mechanisms for public engagement. Average people do not know about checking the *Federal Register* to find open-comment periods or accessing the videocast of this meeting. She noted the challenge is to find a way of listening to people about their concerns and excitement.

Dr. Rudenko said that the Federal Register comment period process does not usually engage people outside of the Capital Beltway. Dr. Marchant said that people often post comments about social values in response to *Federal Register* notices, but the government often does not have the authority to deal with such concerns.

Lorraine M. Albritton, Ph.D., asked for more information about the types of groups to engage. She asked about patient/disease advocacy groups specifically. Dr. Marchant said that those groups would be important, but there are other public groups to consider. He recommended thinking creatively because traditional comment mechanisms do not constitute public engagement. He suggested consulting ethical, legal, and social implications (ELSI) researchers to help with engagement.

Leigh Turner, Ph.D., said that emerging technologies garner attention, but larger ethical issues—such as access to basic health care, equity, and affordability—could serve as touchstones for conversations. Approval of gene therapies and improved cancer treatments cause medical bankruptcies and lead to crowdfunding efforts as people strive to get access to these costly treatments.

Dr. Leshner observed that the issues raised were either generic in nature or idiosyncratic to each technology. When do you go out and talk, and to whom, and what are you going to say? In neuroscience, for example, Dr. Leshner recognized early that topics such as enhancement might cause concerns among the public, but scientists did not want to address these concerns because of the possibility of causing unwarranted agitation. Timing is important when it comes to public engagement, and that is a key reason for involving scientists and developers in planning, but not in the actual public outreach. Dr. Rudenko hoped that the NExTRAC could help identify appropriate venues for talking with people and listening to them about their concerns, then come up with studies to respond to their questions.

Dr. Rudenko spoke about how science is presented in movies and television, and stated that science is often portrayed incorrectly. In the movie*The Martian*, "science"is used as a verb and in the movie *Jurassic Park,* biological containment breaks down, leading to dire consequences. Some work with broadly immersive media (television, movies) needs to be done to stimulate interest in science and impart accurate information. The Science & Entertainment Exchange of the National Academy of Sciences pairs scientists with film personnel and screenwriters.

SESSION II: IDENTIFYING AN EMERGING BIOTECHNOLOGY
The goals of this session were to define key features of novel or exceptional technologies in biomedical science and discuss potential strategies for proactively scanning the research landscape to anticipate their development and application.

The Case for Horizon Scanning
Richard M. Murray, Ph.D.

Dr. Murray discussed past horizon-scanning efforts and some that are ongoing. He also suggested some factors for the NExTRAC to consider for future horizon scans.

National Academies report. Dr. Murray presented highlights of a 2017 report, *Preparing for Future Products of Biotechnology*, published by the National Academies of Sciences, Engineering, and Medicine (NASEM). The authors were charged with identifying likely future products of biotechnology and indicating the scientific capabilities, tools, and expertise necessary to support regulatory agencies. To do so, the authors carried out a horizon scan targeting major advances and potential new types of biotechnology products, excluding human drugs and medical devices.

The report defines biotechnology products as being "developed through genetic engineering or genome engineering or the targeted or *in vitro* manipulation of genetic information of organisms, including plants, animals, and microbes." This included modified nucleic acids and the products of modified organisms. Biotechnology products can be divided into three categories:

- *Open-release products:* products that would be released into the environment, including genetically engineered crops (e.g., BT corn).
- *Contained-use products:* products used in contained areas, such as for industrial fermentation or laboratory use.
- *Platforms:* products, such as CRISPR-Cas9 kits, that are used to make other products.

The scale, scope, and complexity of biotechnology products—and the tempo of their development—are likely to increase in the next five to 10 years , potentially overwhelming the regulatory system. Of greatest concern are biotechnologies of greater complexity with novel risk pathways, such as population and ecosystem engineering, and technologies that are not well understood and lack robust comparators—particularly open-release products, including gene drives, synthetic organisms, and fertilizer probiotics.

The horizon scan identified more than 200 products, along with their estimated development timelines. Information came from the following sources:

- Crowdfunding websites
- Patents
- Press reports
- Previous reports by NASEM
- Publicly available projects developed by International Genetically Engineered Machine (iGEM) teams
- Regulatory agencies' websites
- Scientific literature
- Submitted public comments
- Synthetic Biology Database of products (maintained by the Wilson Center)
- Venture capital company meetings

Dr. Murray said it was challenging to get some companies to talk about what they were working on, but some startups that were seeking potential investors were willing to discuss their products.

New and ongoing efforts related to horizon scanning. Dr. Murray spoke about other horizon-scanning activities, mainly related to synthetic biology:

- The Future Bioengineered Products database has been maintained by the Environmental Law Institute. Dr. Murray suggested that the NExTRAC or other agencies might be able to continue support of this resource, which provides a snapshot of biotechnology development through 2018.
- The Engineering Biology Research Consortium Roadmap, which is based on the design-build-test-learn cycle, is a critical assessment of the current status and potential of engineering biology. The roadmap resulted from contributions of more than 80 scientists and engineers representing a range of disciplines and more than 30 universities and a dozen companies. It provides researchers and other stakeholders (including government funders) with a compelling set of technical challenges and opportunities in the near and long term.
- Shapira P., Kwon S., Youtie J. (2017). "Tracking the emergence of synthetic biology." *Scientometrics,* 112(3):1439–1469.

- Wintle BC, Boehm CR, Rhodes C, et al. (2017). "A transatlantic perspective on 20 emerging issues in biological engineering." *Elife,* 6:e30247.
- Shapira P., Kwon S. (2018). "Synthetic Biology Research and Innovation Profile 2018: Publications and Patents." *bioRxiv* preprint. http://dx.doi.org/10.1101/485805.

Conclusions. For horizon scanning, input should be obtained from a broad variety of sources, including meetings, literature searches, NASEM, and industry organizations. Horizon scanning is a substantial effort that engages industry, academia, and government. The structure for collecting input should be designed to expose gaps in knowledge. Horizon scanning relies on having dedicated staff resources to collect, organize, filter, write, and cajole. It might be possible to leverage multi-agency efforts. Dr. Murray recommended storing information in searchable databases that can be updated, maintained, and queried.

Done correctly, horizon scanning should promote discussion of complex issues before a technology appears, not after. Dr. Murray recommended focusing attention on parts of the future that are more complex and less understood. Absolute timeframes can be wrong, but relative timeframes should be (roughly) correct. The scan results should be updated regularly, perhaps each year.

Lessons from Current Technologies: Genome Editing in the Clinic
Matthew Porteus, M.D., Ph.D.

Dr. Porteus said that genome editing allows changing the DNA sequence of a cell down to the level of a single nucleotide. He explained how nuclease-based strategies—the most well-developed methods of genome editing—work. The nuclease causes a break in the DNA that is repaired by the cell in one of two primary ways. With nonhomologous end-joining (stitching), the result is precise spatial modification, but with homologous recombination, the nuclease cuts the DNA, and then a template of donor DNA is used to introduce exact nucleotide changes at the site of the break.

Based on use of Cas9 nuclease with a guide RNA, nonhomologous end joining or homologous recombination can result in deletions, insertions, or corrections of genes. Additional genome editing tools are being developed that involve different nucleases or non-nuclease based strategies. The precision and ease of genome editng is accelerating the development of agricultural products and may improve the health of humans.

Applications of gene editing to treat human disease. Between 6,000 to 10,000 monogenic diseases exist, affecting about 30 million people in the United States and 350 million people worldwide. Although monogenic diseases are rare, each patient affects a larger community of people and life-years can be saved.

Dr. Porteus discussed *ex vivo* correction of a disease-causing variant that causes sickle cell disease. In the United States, the median lifespan for people with sickle cell disease is in the mid-40s, but in Africa, the lifespan is just 5 to 8 years. Correcting the allele in 20% of hematopoietic stem cells is sufficient to cure the disease, and many treated patients are achieving 60% allele correction. The procedure involves removing stem cells, correcting the genes in the lab, and then

reinfusing the cells into the patient. *In vivo* allele correction is more challenging, but three groups have made two breaks to delete an exon and were able to transform Duchenne muscular dystrophy into the less pathologic form (Becker's muscular dystrophy) of disease. All three groups are moving their process to the clinic.

Other work is improving anti-cancer cell-based therapies by combining genome editing with synthetic biology to enhance the potency of chimeric antigen receptor (CAR) T cells.

Outlook for genome editing. In terms of human genome editing, which applications should or should not be developed? There are also issues of equity and justice; how can we ensure that we do not start thinking of human beings as objects to be engineered or manipulated?

Most countries have ethics systems to deal with somatic cell editing for treating or preventing disease. However, many bioethical issues surround somatic cell editing for enhancement and germline/heritable editing. There is also the challenge of getting high-technology therapies to all patients in the world. Right now, it is still a challenge to get vaccines and antiretroviral therapies into Africa, let alone gene therapy for sickle cell disease. To move forward, social justice and health equity have to be considered.

Throughout history, innovative modalities—such as sanitation, antisepsis, vaccines, small molecules, and biologics—have led to new cures. Now emerging are the living drugs—cell and gene medicines (gene edited or not) and microbiome manipulations. Much work is needed, but these technologies hold the promise of improving patients' lives.

Lessons from Current Technologies: Gene Drives

James P. Collins, Ph.D.

Dr. J. Collins explained that a gene drive is a process of inheritance by which a gene is guaranteed to pass from one generation to the next and, ultimately, throughout a population. The engineered genes are inherited in a biased manner, not conforming to expected Mendelian ratios, such that a trait can spread through a population even if it does nothing good for the individual organism.[3]

Gene-drive technology and its risks and potential benefits. Gene drives are an example of a new technology with uncertain benefits and risks, raising compelling questions at the intersection of science and society. Gene drives occur in many species, although engineered drives will have use only in organisms with sexual reproduction and a short generation time. Gene drives can spread and persist. CRISPR-Cas9 has dramatically altered the ability to generate a gene drive.

Advances in biotechnology are testing the limits of the current regulatory landscape. Proposed applications for gene-drive modified organisms include the elimination of diseases, pest management, agriculture, rescue of endangered species, control of vector-borne diseases, and

[3] Burt A, Trivers R. *Genes in Conflict: The Biology of Selfish Genetic Elements*. Cambridge, MA: Harvard University Press; 2006. Available from: http://roberttrivers.com/Robert_Trivers/Books_files/Genes%20in%20Conflict.pdf

elimination of invasive species. Ethical issues arise because what was once impossible can now be done and, therefore, cannot be ignored. A gene drive could lead to a tipping point, rapidly altering a community. Should humans attempt to alter nature with gene drives?

In 2016, NASEM published a consensus report that found insufficient evidence to support the release of gene drive–modified organisms into the environment. However, the benefits of gene drives for basic and applied research could be significant.

The authors of the NASEM report recommended a phased testing approach, with a series of checkpoints to determine whether and when research should move to the next phase. Each step would provide vital data and knowledge that can be used to inform and enhance the effectiveness of other phases.

Guarding against unintended release or persistence of gene-drive modified organisms would require stringent controls, which could be:

- Biological (fitness cost, insecticide), ecological, environmental, or molecular (split, trans, cutting, repair efficiency, stability over generations)
- Bioinformatics to inform guide RNA targets and predict off-target effects
- Field controls based on split, precision, and threshold drives
- Other safeguards based on drug inducibility or nutrient dependency

The Defense Advanced Research Projects Agency (DARPA) held a Safe Genes workshop in May 2019, during which three types of controls were discussed: control of gene editing through temporal, spatial, and reversible control of gene editors; development of countermeasures and prophylaxis to inhibit unwanted gene-editing activity; and subsequent genetic remediation to remove engineered genes from environments and return to baseline.

Dr. J. Collins said that moving ahead with gene-drive research means integrating values, engagement, and governance. Values can be defined as "deeply held, complicated, sometimes evolving beliefs about what kinds of things—in humans' lives and the world at large—should be fostered, protected, or avoided." The authors of NASEM's report underscored the importance of keeping values front and center and emphasized the role of public engagement (i.e., from communities, stakeholders, and the public). The authors recommended carrying out research addressing values and engagement.

Gene drives' uncertain benefits and risks call for governance that balances a certain degree of precaution against support for science.

Dr. J. Collins demonstrated how heat mapping and word clouds can reveal shifts in the field. Gene drives may be a case of post-normal science: Facts are uncertain, values are in dispute, stakes are high, and decisions are urgent. Before gene-edited organisms are released, we need to take into account the complexity of natural systems, as well as the relevance of human commitments and values.

Neurotechnology

Kafui Dzirasa, M.D., Ph.D.

Dr. Dzirasa reviewed the history of some classic neurotechnologies. Electroconvulsive therapy for depression—a major cause of debilitation worldwide—came into use when it was observed that people with depression felt better after having a seizure. The therapy is highly effective, but the lack of specificity leads to detrimental side effects. A newer type of neurotechnology uses transcranial magnetic stimulation to manipulate magnetic fields and cause electrical pulses. Other indications for brain stimulation are Parkinson's disease, epilepsy, tumors, obsessive compulsive disorder, and depression. Deep brain stimulation is FDA-approved for multiple illnesses, most often Parkinson's disease. This technology is being studied as a possible treatment for pain and major depressive disorder.

Dr. Dzirasa reviewed monitoring technologies for measuring brain activity over time. These include electroencephalography (EEG), magnetic resonance imaging (MRI), and magnetoencephalography (MEG). EEG detects energy at the cranium level, not from within the deep brain. MEG can effectively assess brain activity at slightly deeper levels. Functional MRI serves as a proxy for brain activity based on oxygen utilization, but images are only captured every second, which is slower than the rate thoughts are happening.

Why include neurotechnology in the biotechnologies in the NExTRAC portfolio? Brain disorders, including autism, Alzheimer's disease, depression, cognitive impairment, dementia, Parkinson's disease, and schizophrenia, take a huge toll. Current technologies do not obtain information quickly enough or from sufficiently deep areas of the brain. The advancements of technologies and in understanding of the brain raise issues surrounding how to manipulate or change the brain in more precise ways.

The federal BRAIN Initiative was supported with $300 million at launch in 2013. Through the 21st Century Cures Act and other sources of funding, the initiative has a budget of $4 billion to $5 billion through 2026. The goals are to develop tools to monitor the brain, tools to modulate the human brain (i.e., tools to manipulate brain cells), and analytics and theories to understand it. (New theories could evolve from using AI to detect patterns of brain activity, for example.) The initiative is laying the groundwork to treat brain disorders ranging from autism to Alzheimer's disease.

What will be the next wave of neurotechnolgy? Could smartphones integrate with the brain the same way that pacemakers do for hearts or hearing aids for ears? Several groups outside of NIH are working on such applications. Kernel (a privately held company) is working on neurotechnology; Neuralink (also a company) is developing ultra-high-bandwidth brain–machine interfaces to connect humans and computers; and DARPA is working on bidirectional brain–machine interfaces for controlling unmanned aerial vehicles and active cyber defense systems.

Neuroethics will be important to consider. The BRAIN Neuroethics Subgroup submitted a report to the NIH Advisory Committee to the Director in October 2019 that covered topics such as:

- Privacy concerns
- Autonomy and agency: If people's brains can be controlled, how can they make decisions for themselves?

- Bias
- Applications: If a technology improves memory function, should it be used by university students?
- Moral significance: What is the minimal brain function required to still have all the rights of a human? As we build computers with neurofunction similar to that of human beings, what factors need to be considered?

Synthetic Biology
Christina Smolke, Ph.D.

Synthetic biology (syn bio) represents a tool-driven revolution in engineering biology, comprising three components that can yield new products:

- *Synthesis:* decoupling of design and fabrication, leading to computer-aided design and electronic design apps
- *Standardization:* refined genetic components supporting off-the-shelf reuse of components, thereby greatly increasing the tool's potential impact
- *Abstraction:* engineered simplicity enabling multicomponent systems for engineering new cell components

Synthesis. The synthesis component is inspired by the process of creating natural lineages through breeding of plants and animals, with genetic alterations occurring by mutation or selection. With synthesis platforms, however, genetic changes result from sequencing and editing with intent. The resulting genetic information can then be shared, networked, and synthesized.

Genetic information and genetic material are increasingly interconvertible. Once genetic information is posted in publicly available sequence databases, using informatics solutions, one can search the databases, develop hypotheses, and use synthetic capability to advance science. Syn bio is transforming how science is performed.

Standardization. Standards enable reliable reuse of objects, which requires reliable reuse of performance measurement and modeling. The iGEM competition engages teams of 6,000 undergraduate and high school students from more than 40 countries each year. Over time, iGEM projects have become more sophisticated and support important research, mainly because all teams have to use particular standards for the competition. Setting standards can become a form of governance that could be promulgated globally.

Dr. Smolke explained how measurement standards are supporting new sensor architecture and measurements, enabling the generation of thousands of different sensors that work off the shelf across many systems. Because of standardization, components can be used in many labs for many activities.

Abstraction. As syn bio moves toward more complex biological systems, the question becomes how to make the work easier. Abstraction is a hierarchy that supports "compiling" down to the primary sequence through a series of layers of functional power. This modular approach allows automation through computer programs. Improving the engineering cycle (design, build, test) for biology could drive the cycle faster.

Current challenges in syn bio. Although the cost of DNA synthesis has decreased 100-fold, the technology is still high latency and length limited. The rest of the world is starting to take the lead. Although read–write (sequencing–synthesis) capacities are in place, composition (what and how) lags far behind. Also, synthesis is more advanced than standards and abstractions. Making fundamental improvements in workflow has been a challenge, because everyone is emphasizing applications. Syn bio applications remain expensive and risky: Who will control and own the technology and access to it? Historically, those who lead technology development also lead governance. Many other countries are investing heavily in syn bio and could end up leading governance.

Emerging applications. Scientists are now starting to build complex molecules. With syn bio manufacturing processes, the distributed manufacturing of medicines on demand could become reality.

To develop therapies that really work, sensing capabilities need to be built in to respond to the environment or levels of substances, such as glucose, in the body. Incorporating sensors involves higher levels of complexity.

Panel Discussion with Presenters
Moderator: Alan I. Leshner, Ph.D.

Dr. Leshner posed several questions for the presenters to discuss.

- In terms of developing overarching principles based on what was heard during the presentations, what triggers are there to signal that a technology is somehow special and deserves particular attention? When should that attention be applied?

Dr. Murray spoke of the importance of identifying biotechnologies that are unfamiliar to the regulatory system, technologies that do not seem to fit into the existing regulatory framework. Attention is needed as the biotechnologies start to be deployed. Another trigger might be the development and use of the technologies by nontraditional actors, such as a Kickstarter for a plant that glows. Finally, technologies that are adopted rapidly, such as gene drives and CRISPR, merit special attention.

Dr. Porteus recommended not getting caught up with technologies that bubble up and then die out quickly. When a technology's uptake grows exponentially, that is an important signal. Another signal is when it becomes clear that a technology might change the way science is conducted.

Dr. J. Collins said that, with regard to gene drives, a trigger would occur when a modified organism would have major implications, such as potentially being released into the environment. He recommended engaging historians and philosophers of science who are trained to think about the evolution of ideas. Not all new technologies have immediate implications, but under the right set of conditions, things can take off.

Dr. Dzirasa said that transformative neurotechnology might just be an algorithm that spreads through the internet really quickly and people learn how to make themselves feel happier. At first, neurotechnologies may seem benign, but some of them can damage or destroy lives. He recommended being vigilant in order to observe signals when people can start using a neurotechnology and its use starts to increase.

Dr. Cho agreed about ensuring that horizon scanning includes people who have other backgrounds; for example, sociology backgrounds and people who were with OTA. Social context is very important; the same technology can have very different implications, depending on context.

Dr. Ossorio recently attended a meeting on the potential use of syn bio to address climate change. Social context can change rapidly. For example, climate-related disasters such as fires, hurricanes, and floods might cause the people affected to accept a higher degree of risk. In addition, biotechnologies can have both beneficial and nefarious uses. A recent article in the *New York Times* reported on attempts in China to use DNA samples for facial recognition. This technology could be used for law enforcement or for racial discrimination against Uighurs.

- Virtually every technology is dual use and could have a wide range of applications. What criteria should we impose? How can we assess risk?

Dean A. Lee, M.D., Ph.D., contrasted technologies that create a transient alteration and those that could change who people are as beings, such as through DNA technology. The NExTRAC should think ahead about context and permanence for risk assessment. If CRISPR altered only RNA, it would not permanently alter who we are. Similarly, when it comes to neurotechnology, recording brain activity is one thing, but altering brain activity is different and would require different thinking in terms of risk assessment.

Dr. Dzirasa spoke about critical periods in brain development. We can shape who we are based on how we let the brain develop. Use of screen technology by toddlers means that a device is causing the brain to develop toward a new reward system. Technology has spread everywhere quickly. It is plausible that the human brain might be fundamentally different from the brains of yesteryear.

Dr. Leshner asked about cognitive enhancement, which is of great concern because it would not be equally available to everyone. Does that need particular attention?

Dr. Wolinetz said that products follow a straightforward regulatory pathway. However, when assessing benefits and risks of technologies such as gene drives, it is necessary to think in terms of possible future applications. It is challenging to operationalize oversight and governance in the early stages of development, before regulatory oversight kicks in for a product.

Dr. Porteus advocated maintaining a posture of humility, because long-term consequences are unknown. Incomplete knowledge should be a trigger. If we made a mistake, what would happen?

Dr. Leshner asked whether some technologies are entirely off limits in terms of where society wants to go. Who would make that decision? How could decisions be made early enough to avoid downstream problems?

Benhur Lee, M.D., mentioned brain-controlled exoskeletons that could help soldiers carry 60-pound packs with ease. Some countries might proceed with developing such technologies, and the Department of Defense might want to proceed even if NIH does not. Concerns about germline genome editing have existed since the advent of gene therapy, but one scientist went ahead anyway; three-parent embryos have also been created. Restricting the use of technologies has not been successful. The NExTRAC could lead in considering the implications of novel technologies and applications.

Margaret F. Riley, J.D., said that countries that have the technologies control the governance of the technology. What is the United States funding because it wants control? Once a technology is on the bench, it is out, but we keep thinking about trying to stop technologies (e.g., reverse gene drives). Dr. J. Collins cautioned about "chasing" a technology with a technology; some other solution should be developed.

Ms. Riley said that when a country tries to restrict a technology, the technology often migrates across borders. She suggested that instead of chasing Ph.D. researchers out of the country, we should keep them here to instill and help disseminate norms.

- What are potential strategies for identifying new biotechnologies and their applications, and how can we anticipate these new developments? When has a biotechnology "emerged"?

For horizon scanning, Dr. Murray suggested including products that are probably in development and trying to add some time bounds to reflect when they might come onto the market. Being concrete with timelines, at least in a relative sense, is the best approach.

Dr. Murray recommended thinking globally by considering other countries' social norms and regulatory structure when thinking about horizon scanning. Dr. Cho suggested including nontraditional actors as well. Dr. Dzirasa said that preventing harms could take years. He advised including people with diverse perspectives to speculate about what they foresee as emerging technologies.

Dr. Murray said that the greatest concern centers on technologies that have never been seen before. With subsequent technologies, everyone has a better idea about what to look for and what to ask about. He recommended creating a mechanism whereby complexity and familiarity are important drivers of oversight. More scrutiny is needed for technologies that are not well understood and therefore may present higher levels of risk and require more evidence of safety.

- All technologies carry some risk. How should we decide which ones to worry about? How robust is the existing capability to predict adverse consequences?

Dr. Ossorio commented on existing mechanisms, such as postmarketing drug research, that can accrue evidence about emerging problems. In other domains, however, there is little ability to monitor events and gather data.

Kenneth Oye, Ph.D., said that predicting adverse events associated with emerging technologies is a weak spot. He said that uncertainty is a key factor to consider, and he recommended thinking about observability and feedback about adverse events, because little is known in advance. Another consideration is reversibility. For example, gene drives may offer the potential to cure human diseases, but gene drives are irreversible. Policy needs to support observation and feedback.

Dr. Bloss agreed about starting with uncertainty, but consent is also an issue, particularly with gene drives that might be released into the environment. She recommended that the NExTRAC consider questions of autonomy and people's ability to decide and give consent for technology applications.

Professor Riley remarked on the word "worry." Why is there so little concern about smartphones and AI? Perhaps humans are programmed to worry more about biological changes, such as those brought about through CRISPR technology. Ms. Thiboldeaux agreed that assessing risk depends on risk tolerance, which can differ for technologies, individuals, institutions, communities and countries. Patients are asked every day to make risk assessments about different treatments or participation in a clinical trial, so we need to allow for subjectivity in decision making processes for emerging technologies too. Dr. D. Lee underscored the importance of clarity about risk–benefit analysis and the settings for risk–benefit discussions. The public may focus on the risks of an emerging technology in one setting but focus on its benefits in another circumstance.

- When should a technology be considered have "emerged" by the NExTRAC? What level must a technology reach for regulations and monitoring to be reduced?

Dr. Porteus said that the NExTRAC could consider a technology to have emerged once there is some assurance that the FDA and other regulatory bodies are able to handle regulatory reviews.

Dr. Cho said that questions about societal values and ethics are not evaluated by any regulatory entity. Those value questions come into play through the assessment of risk in the context of benefit. Also, risks and benefits differ for different groups. Dr. J. Collins said that institutional review boards (IRBs) might need an expanded role in deciding whether an institution wants to support certain types of research. However, Dr. Cho said that IRBs cannot consider broad social benefit, so those types of questions are not addressed. Dr. J. Collins said that more consideration needs to be given to the question of where those discussions should occur. Dr. Cho said that other countries are far ahead of the United States in terms of integrating social context in a timely fashion.

Dr. Leshner said it is impossible to know when risks are fully identified; some may come to light later. Dr. Wolinetz also said that some things do not fit neatly into a regulatory configuration. Because of the challenges in "soft" governance strategy, there should be a framework to force

people to pause and think. This would not fit into a policy or regulatory "box," but it would still provide some checks and balances.

Regarding gene drives, Zach N. Adelman, Ph.D., said that a set of standards exists, but there is a lack of knowledge about how to begin evaluating risks. The lack of a consensus is a signal that a technology is still at the emerging stage.

Dr. Porteus suggested identifying biotechnologies that emerged, became pervasive, and caused more harm than good or did not work at all. Dr. Oye said he had worked on such a list in the past. No one effectively predicted beneficial or harmful effects as the technologies emerged. Adaptive approaches are needed because forecasting is not accurate. Dr. Cho agreed that forecasting is difficult, and she advocated creating adaptive mechanisms that include people at the ground level (i.e., working at the bench level in companies).

In regard to negative technologies, Dr. B. Lee recalled that António Egas Moniz, the neurologist who developed the prefrontal lobotomy, received the Nobel Prize for a procedure that is no longer acceptable. Social values are key but differ not only by place but over time. Dr. Gigi Kwik Gronvall agreed that there are many technologies where the original intent was to solve problems with the best methods available at the time but were supplanted by better technologies. Other technologies that we have stepped back from include weapons systems included in disarmament regimes.

Ms. Riley said that a technology will not survive if it does not have utility. She said that once opioids were developed, pain became considered a vital sign and the drugs were considered the greatest thing. But the drugs were overprescribed, leading to an ongoing crisis. It is important to understand an emerging technology's potential ramifications if it were to spread rapidly. Dr. Smolke pointed out that the opioid epidemic is largely a U.S. phenomenon made possible by prescribing practices and a changing social context.

Dr. Turner mentioned the rise of the personal automobile. The invention was greeted with a sense of technological optimism, but now many people feel a sense of ambivalence, because of the destruction of transport systems, degradation of cities, urban sprawl, air pollution, and pedestrian injuries. The investment sector is always forecasting and trying to identify opportunities and spaces. That might be a model for the NExTRAC to ask questions about what spaces or communities might benefit from a technology. For many technologies, there will be some ambiguity, meaning that federal regulations might be too blunt a tool. Dr. Dzirasa emphasized the importance of surveillance and the difficulty of removing something if it is found to cause harm.

Dr. D. Lee said that narcotics and radiation have both horrific consequences and valuable uses. Those technologies are fully emerged, and many systems are in place for monitoring and controlling them. For a technology to be considered emerged, the state of knowledge should be such that safety pieces can be put in place and a plan developed for handling infractions of the rules.

Dr. Wolinetz said that public reaction to embryonic stem cell research and CRISPR technology caught many scientists off guard. Public engagement and thoughtful discussion of oversight are critical when it comes to emerging technologies. How can the NExTRAC help connect all these different pieces?

ADJOURNMENT DAY 1

Dr. Whitley thanked the participants for their useful contributions. The meeting adjourned at 4:45 p.m.

DAY 2

SESSION III: FORECASTING IMPLICATIONS OF EMERGING BIOTECHNOLOGIES

Dr. Whitley called the meeting to order at 9:02 a.m. and introduced the session's objectives: defining the specific risks, benefits, and implications of emerging biotechnologies and discussing strategies for anticipating and addressing these issues.

The Case for Proactive and Adaptive Consideration of Risks and Benefits

Kenneth Oye, Ph.D.

Dr. Oye advocated for creating an adaptive risk governance model by providing some background on prior guidelines and governance efforts, examples of risk prediction, and applications of risk assessment models to current biotechnologies.

Lessons from the 2017 workshop "NIH Guidelines: Honoring the Past, Charting the Future." Dr. Oye said that Dr. Baltimore's keynote address harkened back to the 1975 Asilomar conference. Since then, NIH-funded groups have institutionalized oversight of genetic manipulation, and even institutions not funded by NIH have toed the line. One session during the 2017 workshop focused on emerging biotechnologies, including syn bio, gene drives, and CRISPR gene editing. A concern, however, is whether the existing system of oversight will keep working.

Approaches to risk governance. According to Dr. Oye, there are three main frameworks for risk governance: permissive, precautionary, and proactive/adaptive. Permissive risk governance is based on a rebuttable presumption of benefit. A technology is allowed unless evidence of harm exists. If problems materialize, corrective measures occur after the fact. Precautionary risk governance hinges on a rebuttable presumption of harm. Use of a technology is restricted unless evidence of safety exists. With this model, restrictions may limit experiential learning about benefits and harms. An important challenge with both permissive and precautionary approaches is that they rely on knowledge of benefits and risks, but predictive capabilities are limited.

Proactive/adaptive risk governance first requires preparation by funding research to inform prior probability distributions on benefits and risks. Initial applications with the most favorable priors would be supported. Second, observation would be required to harvest and process information from initial experiences with the technology. Third, adaptation would involve updating or correcting practices as needed, based on credible evidence.

Exemplary cases of proactive/adaptive risk governance include the approach to air safety taken by the Federal Aviation Administration (FAA) and the National Transportation Safety Board (NTSB), the European Union's (EU) transmissible spongiform encephalopathies regulation, and the Environmental Protection Agency's (EPA) Particulate Matter 2.5 (PM2.5) standard. Two examples of cautionary tales are the widespread use of the pesticide DDT, and the FDA's policy on *trans* fats. Both permissive and precautionary approaches rest on the presumptive ability to anticipate benefits and risks.

Dr. Oye supports a proactive/adaptive risk governance model. Initial applications should be based on the fact that no one knows what could happen. The idea is to observe and adapt. For example, the NTSB investigates accidents and near-misses after the fact and only issues voluntary recommendations. The evaluation function conducted by the NTSB is separate from the FAA's regulatory function. This separation of the evaluation and regulatory functions is an approach that should be followed.

Another example is EPA, which has funded studies to capture policy effects. The Six Cities study showed that mortality risk rates dropped as exposures to particulate matter dropped. These findings were translated into policy, followed by litigation and a confirmatory study. Evidence from experimentation was translated into policy.

The EU found that tough regulations to curtail the spread of BSE were not needed, and the laws were relaxed. This is an example of an adaptive risk model in action.

The European Medicines Agency employs an adaptive licensing approach whereby patient experience contributes to evidence development after registration of a new drug. Front-end (premarket) studies are limited to a subset of patients most likely to have benefit to reduce exposure to the agent under study. Back-end (postmarket) registries and studies track the wider patient experience after drug licensure. This model has been adopted not only in the EU but also Canada and Japan for certain medicines and devices.

Applications of current biotechnology. Dr. Oye said that risks stem from uncertainty, observability, and reversibility. Unobservable and unknown risks are his greatest concerns. Information on genetic technologies is copious and is being deposited in data banks. The cost of DNA sequencing has decreased dramatically. The result is an explosion of emerging applications in four main areas:

- *Agriculture and aquaculture:* Examples include gene-edited salmon that grow year-round, demonstration of CRISPR-Cas9 technology in larger mammals such as goats to produce cashmere, and gene editing in pigs to make the animals resistant to African swine fever.
- *Industry:* Examples include synthesis of organic materials for vaccine development and production, and complete biosynthesis of opioids in yeast.
- *Medicine:* Examples include somatic cell gene therapy for sickle cell disease, thalassemia, cystic fibrosis, and hemophilia. Regenerative medicine based on xenotransplantation is of concern because of the potential for overlooking porcine retroviruses that end up in humans. Also, the potential alteration of behavioral genes presents special concerns. Germline gene therapy is worrisome because the genetic changes are heritable. Some researchers have proceeded with germline gene therapy in humans despite these concerns and the guidelines prohibiting this sort of research.
- *Environment:* Emerging applications include pollution remediation and use of gene drives to control invasive species and insect vectors of disease. Unintended effects are a risk.

Most researchers are acting responsibly and adhering to guidelines to safeguard their experiments. Research funders are issuing guidelines as well. Dr. Oye recommended workshops for evaluating designs and test methods. Those who are proposing, conducting, or funding emerging technologies have a duty to evaluate their actions with regard to both legal standards and ethical norms. Obligations follow from that duty:

- Align one's own work with laws and norms based on existing knowledge.
- Encourage others to align their work with laws and norms.
- Identify key gaps in existing knowledge, and fill gaps through research.
- Identify key gaps in legal coverage, and join the debate on gaps.

In a 2017 editorial,[4] Dr. Oye and co-authors issued several recommendations for NIH to consider, including the following:

- Reach non-NIH-funded actors.
- Foster researcher and funder guidance.
- Establish oversight mechanisms that address risks beyond select agents.
- Source DNA from the synthesizers within the International Gene Synthesis Consortium.
- Support adaptive learning and reassessment by using the institutional biosafety committees (IBCs) as "eyes and ears"; pooling information via the WHO, the Biological Warfare Convention, and other entities; funding research on potential risks; identifying and filling oversight gaps; and using information to modify voluntary and mandatory oversight.

Weighing Risks (Hazards) and Benefits of Gene-Drive Technology: Lessons from Biosafety
Zach N. Adelman, Ph.D.

Gene drives are not new; meiotic drive systems have been around since 1976. However, this technology is now more accessible.

Dr. Adelman clarified that gene drives do not break the laws of inheritance. With a homing-based gene drive, the mode of inheritance is the same as with Mendelian inheritance, but 100% of gametes carry the transgene instead of 50%. Depending on the target of a homing gene drive, the risk can be nil, as is the case when the target does not exist in nature. If the target is a mosquito gene involved in female sex determination, then the risk of spread in the environment is substantial, since the target exists in the wild population and resistance was not selected for in laboratory populations. Dr. Adelman said these examples show how the same technology can lead to very different risk profiles based on the potential for spread in the environment.

"Gene drive" is a term that has limited utility as a starting point for risk assessment; gene drive is just a description of an agent. Regardless of the agent, the underpinnings of risk assessment remain the same, centering on questions about whether the agent could harm workers, the community, or the shared environment. Although the answers to those questions change, the questions themselves do not. Dr. Adelman added that any attempt to begin risk assessment based on the use of a particular technology has little chance of keeping up.

[4] Oye KA, O'Leary M, Riley MF. (2017). Revisit NIH biosafety guidelines. *Science*, 357(6352):627. doi:10.1126/science.aao6398

Biosafety guidance and oversight for research involving recombinant or synthetic nucleic acids has been provided through implementation of the *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules*. However, the world has changed since the original guidelines were issued, and the hierarchy of four risk groups no longer directly applies to all emerging technologies. Dr. Adelman proposed an updated starting point for risk assessment of laboratory-based transgenic organisms based on whether the introduced transgene is likely to persist or spread through a natural population if introduced. Natural selection would eliminate a transgene if it did not provide a benefit to the species. Containment conditions and practices should be set on a case-by-case basis.

Institutional review of transgenic arthropod research. Transgenic arthropods themselves present little risk to the health and safety of laboratory workers and therefore might not be given as thorough a review as pathogen-based work or human gene therapy. Neither the *NIH Guidelines* nor CDC/NIH *Biosafety in Microbiological and Biomedical Laboratories* provides sufficient guidance on containment of arthropods such as beetles, wasps, and flies. Also, research investigators have varying levels of familiarity with guidelines and principles. Dr. Adelman pointed out that protecting those closest to the danger also protects everyone else. However, if a technology's primary impact is on the environment or on human values, protection of laboratory personnel is not enough. Risk assessments must be rigorous enough to cover those situations.

Currently, risk assessment groups focus on protecting human health. IBCs rarely have representation of experts in entomology, biologic controls, USDA quarantine, ecology, and invasive species. He suggested that this needs to be more formalized to protect the shared environment.

Containment practices. Little specific guidance for arthropod containment is available. In 2003, the American Society of Tropical Medicine and Hygiene developed a set of arthropod containment guidelines (ACGs), which are not binding and are not consistently used by investigators or IBCs. The ACGs do not mention gene drives, but current interpretations usually have designated these transgenic organisms as arthropod containment level 2 (ACL-2) or ACL-3. Protection of workers does not require all the protections of a level-3 facility, but safety features usually include controlled access, inward airflow, secure primary containment, traps, solid waste disinfection, activity isolation, sealed windows, and so forth.[5]

Risk management. Risk management of gene-drive transgenic organisms is no different from work with pathogens, but as the potential hazard of a technology increases, so should risk management strategies. Beyond engineering controls, safety measures often include the following:

- Work practices (standard operating procedures, biosafety manuals)
- Safety equipment
- Personal protective equipment
- Training

[5] Benedict MQ, Burt A, Capurro ML, et al. (2018). Recommendations for laboratory containment and management of gene drive systems in arthropods. *Vector Borne Zoonotic Dis*, 18(1):2–13. doi:10.1089/vbz.2017.2121

- Facility design
- Security

Some genetic mitigation approaches are experimental; as such, they need to be evaluated and independently validated. The list of potential mitigation technologies includes kill switches, inducible triggers, split drives, and synthetic target sites. Of primary importance is establishing a culture of safety among technicians, postdoctoral candidates, and associate and principal investigators to make sure the work is done safely.

Stakeholder Engagement

Cinnamon Bloss, Ph.D.

Dr. Bloss mentioned a docuseries released on Netflix, *Unnatural Selection,* which covers topics such as patients awaiting approval of gene therapies, biohackers, DIY individuals with an interest in CRISPR, concerned scientists, and an Aftrican country that may become one of the first field trial sites for a gene drive. Given that Netflix has more than 151 million subscribers, this is a powerful way to communicate. (In comparison, the *New York Times* has 35 million paid subscribers.) Clearly, people are learning about new technologies in novel ways.

According to data collected by the Pew Research Center in 2018, the public is open to new technologies, including some applications in animals and humans. However, people are concerned about potential negative effects.

Background on engagement. The engagement field is relatively new. Variations in definitions, language, and concepts contribute to a lack of clarity. Other challenges include vaguely articulated goals for engagement, failure to disseminate engagement projects for novel technologies, and a lack of ways to incorporate engagement results into decision making.

The Centers for Disease Control and Prevention published the *Principles of Community Engagement* in 1997. The Community Advisory Board model was developed at NIH in the 1990s and built upon the idea that HIV/AIDS communities and advocacy groups should have a meaningful role in HIV/AIDS research. NASEM, the WHO, and the Foundation for the National Institutes of Health have developed guidance about engaging various audiences in the context of gene-drive trials, but it is clear that engagement means different things to different organizations.

Dr. Bloss pointed out that audiences exist on a continuum:[6]

- *Public audiences:* groups of people who contribute to democratic decision making but lack direct connection to gene drives
- *Stakeholders:* people with direct professional or personal interest in gene drives
- *Communities:* groups of people who live in or near candidate release sites for gene-drive organisms

[6] "Engaging Communities, Stakeholders, and Publics." In: National Academies of Sciences, Engineering, and Medicine. *Gene Drives on the Horizon: Advancing Science, Navigating Uncertainty, and Aligning Research with Public Values.* Washington, DC: The National Academies Press; 2016. https://doi.org/10.17226/23405.

There is some tension and confusion between engagement and consent. If a project does not include individual informed consent, then engagement is all the more important. Evidence suggests that Americans' current level of trust in scientists is high, but there are broad trends toward democratization of knowledge, expertise, and decision making. Engagement is expected.

Dr. Bloss gave an example of how public input can influence outcomes. Genetically engineered Oxitec mosquitoes were developed in 2009 in response to a dengue outbreak. In 2011, release of Oxitec mosquitoes was planned and announced for Key Haven, Florida. Despite community engagement efforts, some residents were strongly opposed to the field trial. During the FDA's public notice and comment period, 74% of comments opposed the project. The trial did not go forward.

Engagement typology for genetic engineering in vector control. Dr. Bloss described an effort to organize activities into a typology based on easily identified and relevant features to identify lessons for future work. Through key informant interviews and analysis of documented examples of engagement, Dr. Bloss and colleagues identified 23 unique examples of engagement projects, but only 14 had been documented and disseminated. The authors compared the examples in terms of timing, initiators, target groups, methods, goals, and other features. No clear patterns emerged with timing. Methods were not related to the target groups, and goals were often poorly articulated and not matched to the method.[7]

Current example of engagement for a gene-drive project for vector control. Dr. Bloss provided some background on the 2017 DARPA Safe Genes Program. Team California consisted of a multidisciplinary group of University of California investigators who were seeking a way to safely engineer various classes of gene drives to control a major invasive disease vector, the *Aedes aegypti* mosquito. Team California assessed California residents' general responses to gene-drive systems under development and sought to identify whether those responses would be actionable by Team California scientists. The engagement effort was designed to incorporate engagement results into research, aimed for well-articulated goals and planned dissemination, and tried to use novel methods of engagement.

The investigators used online chat focus groups and a narrated slideshow series to engage participants. This type of engagement allowed for easier access to the material and helped to ensure that the explanation of what might otherwise be a very complicated technology to be presented to all focus groups in the same way every time. Key considerations for developing these engagement methods included language choice and metaphors. In California, there are 15 million Spanish speakers; however, because of concerns about translating evolving English-language concepts into another language, the materials were disseminated via English-language outlets. The effectiveness of the methods did not seem to be delimited by language/literacy, however.

Eighteen focus groups involved 136 participants. Questions from participants dealt with the role of mosquitoes in the ecosystem, specifics of the method, and that the mosquitoes should be

[7] Schairer CE, Taitingfong R, Akbari OS, Bloss CS. (2019). A typology of community and stakeholder engagement based on documented examples in the field of novel vector control. *PLoS Negl Trop Dis*, 13(11):e0007863. doi:10.1371/journal.pntd.0007863

confined or a mechanism to retrive the gene drive-mosquitoes should exist (call-back), even if confinement or call-back results in a more expensive study. Follow-up work to gauge scientists' reactions to the focus group feedback is underway. However, almost no studies in the literature present information on scientists' perceptions of the utility of engagement work. However, engagement could influence how results are communicated and how public health professionals could use the results. Less clear to scientists is the value of engagement in influencing laboratory-based work, now or in the future.

Engagement of the future. Dr. Bloss recommended using new communication tools for engagement while keeping in mind cultural, geographic, and linguistic diversity. She also spoke about the importance of matching engagement to the phase of the technology. (See the table below.)

When communicating about science, it is important to understand that explaining science does not translate into more public support. The Knowledge Deficit Model has proven ineffective for a wide range of scientific issues, including genetic engineering. Individuals interpret information based on their preexisting values, experiences, interests, and perceptions. Dr. Bloss introduced the concept of community-reported outcomes that reflect what matters to communities regarding research on gene drives or other emerging biotechnologies. Risks and benefits are often unknown, but stakeholder interests and values can be elucidated and measured systematically. She also thought that augmenting environmental assessment with systematic social assessment (e.g., using community-reported outcome measures) could more authentically contribute to regulatory review.

Development Phase	Audiences	Message	Inquiry
I. Research to Proof of Concept	Popular, science, and business press; students; colleagues	We have a promising technology, but there is still much to learn.	Who might benefit from the technology? Who will **decide** whether it should be used?
II. Seeking Field Trial Site	Local leaders, residents	We think our technology will help with a problem you have, but we have to test it.	Will **local** political **interests** support a field trial?
III. Seeking Regulatory Approval	Regulators; local leaders; residents; popular, science, and business press	We are committed to designing responsible tests of safety.	Are regulatory agencies **trusted** to make a fair assessment?
IV. Field Testing	Residents	Regulators and local leaders agree this test poses limited risks.	What are residents' **concerns** about the trial?
V. Bringing to Market	Potential customers and their constituents	We have a solution to your problems.	Who decides whether to **purchase** the technology?

Dr. Bloss suggested the following steps for engaging with audiences on gene-drive projects:

- Establish goals and choose engagement methods linked to those goals.
- Consider the three "whys" of engagement (inquire, influence, involve). The "who" and the "how" will flow from the "whys."

- Match engagement to the development phase.
- Disseminate engagement projects to build an evidence base.

Panel Discussion with Presenters
Moderator: Margaret F. Riley, J.D.

Ms. Riley thanked OSP leaders for organizing this meeting and summarized the preceding presentations. The panel discussion centered on three questions.

- How can we identify emerging biotechnologies that may pose novel risks, benefits, and oversight challenges?

Dr. Oye remarked that many new technologies and novel actors do not fit into the existing framework of regulations and guidance. Horizon scanning can help with proactively engaging with actors that are already understood, but it is very important to reach non–NIH-funded actors. He suggested developing researcher and funder guidance to provide some structure. This is happening to a certain extent with gene drives. The challenge is uncertainty and strange new things; that is where adaptive learning and reassessment come in. Biosafety officers protect public health and can be sources of information about what is going on in various institutions.

Dr. Oye discussed the need to pool information where people get together and talk. The challenge of emerging technologies is not unique to the United States. He suggested funding research on potential risks. The NExTRAC is well positioned for identifying oversight gaps. Some risks might be managed voluntarily within the existing regulatory framework, but there are some gaps that may necessitate regulatory changes.

Dr. Adelman said that, on the local level, a more adaptive framework would include mechanisms for easy and continuing interactions between principal investigators and IBCs and biosafety officers. Regarding risk assessment, an outcome-based focus is needed not an assessment of individual components.

Dr. Ossorio discussed voluntary restraints versus mandatory oversight. Her idea was to start with voluntary restraints, such as accreditation and NIH conditions of funding, and then test their effectiveness to identify successful strategies. Mandatory oversight could include FDA regulations. For voluntary guidelines for activities such as heritable gene editing, it is important to keep in mind that there are different professional societies and different actors. Researchers from around the world want to collaborate and publish; they do not want to be "outlaws." However, people who run reproductive clinics, for example, might not be swayed by voluntary guidelines, due to a different set of incentives. For stem cell clinics, although the FDA says it has jurisdiction, the agency has tremendous problems regulating this sort of activity.

Dr. Adelman said that problems are more likely to occur when people come up through a community not accustomed to standards. There are gaps between people working solely in the lab following established standards, the people who are developing products who may not be aware of community standards but follow regulations, and people who want to test outside of the lab but are not developing products. The system is not set up to cover those gaps.

Dr. D. Lee underscored the importance of systematic and robust collection of data for learning and reassessment, which are critical to an adaptive regulatory system. When the RAC went away, there were concerns about moving away from centralization of data and expertise toward the IBC model. What kinds of data do we need when technologies are used to manipulate people's brains or create gene drives? Dr. Oye suggested being strategic about additional research to generate information for appropriate decision making on policy problems. He recalled how the EPA used research findings to support policy making. Fragmented, disorganized data are not useful.

Dr. Adelman said that IBCs should integrate data either horizontally across institutions or in an integrated way through a body such as the RAC.

- What ethical and social issues do emerging biotechnologies and their applications have in common with established technologies? What issues are different?

Ms. Riley said that local reviews by IBCs and IRBs are constrained with regard to the ethical issues they can engage with. The FDA does not act on ethical concerns or values. She mentioned ELSI programs and the need to cover benefits as well as risks.

Dr. Oye said that individual scientists have to account for what they are doing. Faculty should engage on these ethical issues, but teaching scientists and engineers to think deep thoughts is not a satisfying endeavor. Ethics are contextually sensitive, adding to the challenge of discussing the ethics of technologies with international implications.

Dr. Bloss tends to look at things from a public health standpoint when it comes to vector control and from an individual standpoint for medical research. With dual-use research, there is a distribution of risks and benefits. Phase I trials are designed to identify risks and benefits, but for new technologies, the risks and benefits are at a community scale. There is no way for a person to opt out or give individual consent. Public health ethics is a new field.

Dr. Adelman clarified that IBCs do not include an ethical component. Community members of IBCs often have public health backgrounds or are people who retired from the institution. Ethics input is needed. He thought that scientists might object if research did not move forward because of community concerns.

- How do we engage the public effectively in discourse, especially at early stages when specific applications or safety challenges might not be known?

Dr. Bloss spoke in terms of general principles that would apply to all engagement efforts across all technologies. She suggested both a goal-oriented approach to encourage people to be explicit about what they are trying to accomplish and providing incentives for engagement. For the most part, those two concepts are universal and are considered engagement best practices. She advised taking a phased approach by being deliberate and explicit regarding engagement during early versus late stages of research. With the Team California project, she has been learning about

differences in people's transparency about their plans. Decision making should be based on the public's best interest.

Dr. Leshner said that engagement does not mean simply trying to get people in the community to agree with what scientists want to do. He recommended setting some goals proactively: What will be done with input from the community? Would the research be stopped if the community objected to it? Dr. Leshner underscored the importance of being clear about the objectives and process for community engagement and being explicit about what would be done with the results.

Dr. Bloss agreed about thinking prospectively about the aims of engagement work: "If you want to learn something, establish your methods. If you are trying to influence a community, be explicit." She suggested starting engagement during the early stages of technology development and having the initiators of engagement help prepare scientists for engagement work and encourage them to be open to different outcomes. Dr. Oye supported the idea of involving community members and empowering players to act based on the outcome of engagement.

Dr. Whitley spoke about the effect of changing contexts. An outbreak can change the landscape and stakeholders' interests. For example, gene-drive research aimed at reducing mosquito populations in Florida met with community opposition, but when Zika virus started to affect the local population, the community became more amenable to the research.

Dr. D. Lee asked for examples of engagement that could have been done better. The NExTRAC is talking about technologies and policies writ large, not specific projects. What should the NExTRAC's specific goals be with regard to engagement? What is adequate engagement? How would the NExTRAC know when community engagement is complete?

Dr. Bloss suggested thinking conceptually about the goals of engagement at different phases of technology development and specifying goals so it is clear when the goals have been achieved.

Regarding stakeholders and ethical considerations for gene drive technology, Dr. Oye recommended thinking in terms of local versus global measures. The scope of participation and ethics discussions could be limited for a localized gene drive. Some of the most technical topics require engagement and evaluation, which recursively influence who should be at the table. But first, it is necessary to have extensive discussions with a wide range of groups to come up with credible assessment of local versus global concerns.

Dr. Cho discussed using a layered approach for community engagement to build and expand a culture of safety. She agreed with Dr. Bloss about the lack of attention given to the effects of community engagement on scientists. Dr. Cho recommended helping scientists better understand the value of community engagement. Human values should be included in what is done at the scientific bench. The Clinical and Translational Science Award (CTSA) Program encompasses ethics consultation services at awardee institutions, but individual scientists and research administrators are responsible for identifying potential ethical issues. Ethics consultation services might be an early detection system for technologies that are popping up but have not yet been developed. Scientists recognize the need for consultation. Dr. Cho highlighted a recent example

of community consultation that was integrated into studies of sexual behavior in genome-wide association studies.

Dr. Oye said that the genomics of behavior is another important point to discuss. Deciding who should take part in that discussion is challenging. Oversight by political authority could be very dangerous, and there is a risk that results could be misused. Entities such as the NExTRAC could have an important role in deciding what research is correct, based on the uncertain information about potential effects.

Dr. Dzirasa suggested thinking more broadly about community by bringing more people into the discussions about setting standards and norms. He recommended engaging a broad set of people, including high school students, to establish "cultural norms."

Ms. Thiboldeaux recommended asking communities how they want to be engaged and looking at examples of community engagement that worked or failed. She suggested that the NExTRAC members examine their institutional models for engagement. More input is needed for these early discussions.

Ms. Riley supported the idea of how some entities use advanced technologies for engagement. Netflix, for example, has a broad reach but it does not support two-way dialogue. Each technology is new and has a developing code of ethics. Scientific publishing has a 100-year-old code of ethics. The NExTRAC should think about how the ethics behind the technologies are evolving. Dr. Bloss said that using technology to study technology offers many opportunities, noting that thousands of people commented on the Netflix docuseries *Unnatural Selection.* This could be an example of engagement and how people are learning about technologies.

Dr. Oye cautioned that modern communication technology is fragmented and polarizing. People communicate with those who think like them, not with people who have other viewpoints. Regarding engagement, there is a risk that extreme viewpoints could persist and be impossible to reconcile. The challenge is greater now than it was five years ago. He asked what is learned from calls for public comments to the *Federal Register* notices.

Dr. Tucker said that the comments are a useful marker to get an idea about how people feel about an issue, but some comments are not as useful for decision making as others. Dr. Wolinetz said that the comments often provide a snapshot of people who are already engaged on an issue.

Dr. Wolinetz brought up the concept of stewardship. NIH has a unique role as a public funder of research; this brings a unique obligation. For publicly funded research, community engagement is a must.

Dr. Oye said that NIH is a public agency fostering publicly funded research, but it is not the only source of funding. The decisions and guidance that come from NIH are not binding on all researchers. Extending guidance over other actors is challenging.

Dr. Adelman said that stewardship goes along with the culture of safety. Much of science is funded by the public, and the public trusts scientists to do the work safely. Scientists whose work

is funded by taxpayers must understand and buy into the fact that earning and keeping the public trust is paramount. However, some actors work in their own interest, not the public's.

Dr. Bloss agreed that stakeholders in emerging technologies are a highly diverse group, including people involved in DIY projects and the taxpaying public. The NExTRAC's work should be widely disseminated and publicly available.

PUBLIC COMMENTS

Dr. Whitley suggested that people participating via the videocast send their comments to Dr. Tucker by email within the next 10 days. He extended an invitation to people in the room to use the microphone to deliver their comments.

Gerald Epstein, Ph.D., a Distinguished Research Fellow with the National Defense University's Center for the Study of Weapons of Mass Destruction, raised several points. Dr, Epstein indicated he was not speaking on behalf of the National Defense University.

- When is a technology no longer considered "emerging" and no longer in need of oversight? Dr. Epstein said that the degree of certainty about risks is an important factor; the need for oversight does not equate with emergence.
- Assessment of a risk does not imply that any particular policy approach should be employed to deal with the risk. Dr. Epstein suggested analyzing problems and then figuring out what to do about them.
- Recognize that evidence may not be available. It is sometimes necessary to go by plausible analysis instead of evidence.
- Regarding the idea of enforced thoughtfulness, aspire to obtain a variety of perspectives, including from those who are not getting direct benefit.

CHARGE TO NExTRAC

Francis S. Collins, M.D., Ph.D.

Dr. F. Collins said it is unusual to deliver a charge to a group at the end of a two-day meeting, but it was important to have the NExTRAC focus many important issues, including stakeholder involvement, before the charge was delivered .

Dr. F. Collins charged the NExTRAC with forming two working groups:

- One to establish a framework for a thoughtful approach to assess the potential issues associated with new biotechnologies and their applications
- One to assist in the development of a path forward for biomedical research involving genedrive–modified organisms

The working groups should report back to the NExTRAC during the next public meeting. Most likely, the NExTRAC Framework Working Group will consist only of NExTRAC members, and the Gene Drives in Biomedical Research Working Group will include outside experts in addition to NExTRAC members.

Charge to the NExTRAC Framework Working Group

Dr. F. Collins outlined the charge to this working group:

- Describe effective approaches for prospectively identifying emerging biotechnologies or specific applications with reasonable potential to have important scientific, safety, or ethical considerations.
- Conceptualize a framework for the NExTRAC's deliberation of issues surrounding emerging biotechnologies and applications, including:
    - Establishing guiding principles for when an emerging biotechnology or its applications would significantly benefit from further public deliberation
    - Creating a potential process by which the NExTRAC will consider or evaluate any given emerging biotechnology or its applications

The NExTRAC Framework Working Group should consider the following:

- Applications of emerging biotechnologies, given that the way the biotechnology is used often generates the safety, social, or ethical issues
- Effective horizon scanning approaches, focusing on biotechnologies and applications that are reasonably anticipated versus hypothetical
- Cross-cutting issues that may be relevant for a variety of emerging biotechnologies and applications
- Strategies for committee engagement and soliciting feedback

Dr. F. Collins asked that the NExTRAC Framework Working Group discuss whether other groups are already conducting these activities and whether the activities fit within the NIH mission. It is important to avoid duplicative effort. Is there a path forward that would result in a useful outcome, as opposed to an academic discussion? He asked that the working group produce actionable recommendations and insights.

Charge to the Gene Drives in Biomedical Research Working Group

Dr. F. Collins outlined the charge to this working group:

- Consider whether existing biosafety guidance is adequate for contained laboratory research utilizing gene-drive technology
- Outline conditions (if any) under which NIH could consider supporting field release of gene-drive–modified organisms
- Provide advice on the following issues:
    - Given the diverse applications and species that may be used in gene drive research with different risks, is the current landscape of biosafety guidance adequate for contained research?
    - What knowledge and conditions should be in place to help ensure that field-release research of gene-drive–modified organisms could be conducted safely and ethically?

Timeline

1. January 2020: Establish the two NExTRAC working groups.
2. Summer–Fall of 2020: The NExTRAC Framework Working Group presents its draft report at a NExTRAC meeting.
3. Summer–Fall of 2020: Convene a workshop for the Gene Drives in Biomedical Research Working Group.

4. Fall–Winter of 2020–2021: The Gene Drives in Biomedical Research Working Group presents its draft report at a NExTRAC meeting.

Discussion
Dr. Adelman asked whether the working group on gene drives would be addressing other technologies (e.g., gain-of-function experiments, inserting genes for insecticide resistance into butterfly species) that might be more invasive than gene drives. Dr. Wolinetz said that the working group should focus on NIH's mission space. If it considers a set of issues important and within NIH's mission, the working group could make recommendations. Dr. Oye said that some technologies could be considered as alternatives to gene drive technology. Also, localized (in addition to global) systems should be within the purview of the Gene Drives working group.

Dr. Ossorio asked about the availability of processes and staff resources to support horizon scanning, a labor-intensive effort. Dr. F. Collins thought that Dr. Tucker could help mobilize expertise and resources within the Office of Science Policy.

Dr. Turner asked about the context for selecting these two working groups and generating their charges. What might the NExTRAC do in the future beyond these specific tasks? Dr. F. Collins said he is looking to the NExTRAC for guidance. Since other groups, including the WHO and the National Academy, are delving into germline gene editing the NExTRAC will only likely be involved if it could provide some unique advice and if its work would not be duplicative. The NExTRAC will probably want to get into the neurotechnology area. For gene drives, the Gates Foundation is supportive and moving ahead rapidly.

NEXT STEPS
Carrie D. Wolinetz, Ph.D., and Richard Whitley, M.D.

Dr. Wolinetz said that she and others will reach out to the NExTRAC members to identify volunteers and co-chairs to serve on the working groups and to nominate individuals who could serve as *ad hoc* experts. The next meeting will likely occur during the summer or fall of 2020. More information will be forthcoming.

Dr. Wolinetz and Dr. Whitley expressed their gratitude for the hard work that went into organizing this meeting. They thanked the participants, panelists, presenters, NExTRAC members, and everyone who watched via the videocast.

ADJOURNMENT
Dr. Whitley adjourned the meeting at 12:30 p.m.

3/6/2020

Jessica Tucker, Ph.D.
NExTRAC Executive Secretary

I hereby acknowledge that, to the best of my knowledge, the foregoing Minutes and the following Attachments are accurate and complete.

This Minutes document will be considered formally by the NExTRAC; any corrections or notations will be incorporated into the Minutes.

Date: Mar. 6, 2020

Richard Whitley, M.D.
Chair, Novel and Exceptional Technology and Research Advisory Committee

ACRONYMS AND ABBREVIATIONS

ACG	arthropod containment guidelines
ACL	arthropod containment level
AI	artificial intelligence
BRAIN	Brain Research through Advancing Innovative Neurotechnologies®
BSE	bovine spongiform encephalopathy
CAR	chimeric antigen receptor
COI	conflict of interest
CRISPR	clustered regularly interspaced short palindromic repeats
CTSA	Clinical and Translational Science Awards
DARPA	Defense Advanced Research Projects Agency
DIY	do-it-yourself
EEG	electroencephalography
ELSI	ethical, legal, and social implications
EPA	Environmental Protection Agency
EU	European Union
FAA	Federal Aviation Administration
FDA	Food and Drug Administration
IBC	institutional biosafety committee
iGEM	International Genetically Engineered Machine
IRB	institutional review board
MEG	magnetoencephalography
MRI	magnetic resonance imaging
NASEM	National Academies of Sciences, Engineering, and Medicine
NIH	National Institutes of Health
NExTRAC	Novel and Exceptional Technology and Research Advisory Committee
NTSB	National Transportation Safety Board
OSP	Office of Science Policy
OTA	Office of Technology Assessment
PM2.5	particulate matter 2.5 (micrometers in diameter)
RAC	Recombinant DNA Advisory Committee
Syn bio	synthetic biology
USDA	U.S. Department of Agriculture
WHO	World Health Organization

Attachment I:
Novel and Exceptional Technology and Research Advisory Committee Roster

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