ON REVISION OF THE COORDINATED FRAMEWORK FOR THE REGULATION OF BIOTECHNOLOGY

A White Paper prepared for consideration by the Biotechnology Working Group
U.S. Emerging Technologies Interagency Policy Coordination Committee

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PART ONE: PRIORITY REGULATORY ISSUES – RESPONSES TO QUESTIONS IN REQUEST FOR COMMENT

On October 5, 2015, the Biotechnology Working Group issued a request for public comment to support updating of the Coordinated Framework on Biotechnology. This section treats each of the five priority questions in turn, with:

- Analysis of public comments to date, identifying issues extensively discussed (by which actors);
- Identification of issues for deliberation and resources for biotechnology working group; and
- Provision of our recommendations.

A more extensive analysis of public comments is included as Appendix A to this report.

Question 1. What additional clarification could be provided regarding which biotechnology product areas are within the statutory authority and responsibility of each agency?

a. The Coordinated Framework assigns regulation of biotechnology products to agencies and places it under legislation already responsible for regulating related non-biotechnology substances. The Food and Drug Administration is charged with regulating genetically modified food, food additives, and human and animal drugs, among other substances, under various existing legislative acts. USDA regulates genetically modified plants and animals. EPA regulates microbial pesticides under the Federal Insecticide Fungicide and Rodenticide Act, as well as other recombinant DNA microbes and algae "intended for general commercial and environmental applications" under TSCA.[17]

b. Some new applications cut across boundaries that define the purview of agencies, some do not fall within the purview of any agency, and some applications that fall clearly within the purview of an agency do not fit within the definitions and standards of the relevant agency. These issues are treated in detail in responses to the questions 2 and 5 below.

c. Additional clarification on the statutory authority and responsibility of agencies should be provided in a timely manner with a brief explanation of the basis for decisions.

(1) firms with products that do not fall clearly within the purview of an agency need a clear point of entry and timetable to secure clarification on which agency or agencies will serve as lead;

(2) the Biotechnology Working Group should be designated as the point of entry in such instances and be constituted on a permanent basis;

(3) firms should receive answers to queries on jurisdiction in a timely manner, not to exceed one month;

(4) statements describing the basis for decisions on designation of a lead agency or agencies should be part of the public record to provide evolving guidance for developers of new biotechnology products.

Question 2. What additional clarification could be provided regarding the roles that each agency plays for different biotechnology product areas, particularly for those product areas that fall within the responsibility of multiple agencies, and how those roles relate to each other in the course of a regulatory assessment?

a. Some emerging applications of biotechnology use new methods to accomplish unconventional ends, such as editing the genes of wild populations, not anticipated when the Coordinated Framework was first promulgated. Most current applications of biotechnology use new methods to accomplish conventional ends, such synthesizing materials or changing the properties of crops. Both unconventional and conventional applications cut across existing jurisdictional boundaries of USDA, EPA and FDA and raise issues that fall beyond the purview of these agencies.

b. Gene drives are being developed to suppress invasive species and control vector borne diseases by driving genetic alternations through wild populations of sexually reproducing plants and animals. In anticipation of these potential applications, we published "Regulating Gene Drives" in *Science* in 2014,

and worked with potentially interested agencies and boards to identify who would regulate such organisms under what statutes and regulations.[12]

- FDA has responsibility for evaluating genetically engineered DNA constructs intended to affect animals under provisions for veterinary medicines.
- USDA could be involved if alterations will have effects on livestock or crops.
- EPA has broad responsibility for environmental implications of alterations, through in practice EPA TSCA assessments focus on microbes and algae.
- State authorities have expressed an interest in evaluating potential applications with reference to local environmental effects.
- Other boards and agencies have expressed an interest in assessment and mitigation of biosecurity implications. To date, these have included NSABB, the FBI, DHS, DTRA, DARPA and the National Intelligence Board.
- All Federal and State agencies underscored the need for information on gene drive mechanisms, environmental and security effects, and technical features to limit potential environmental and security effects, including immunization drives and reversal drives.

c. Bacteria, yeast and algae are currently being used to produce high value drugs, scents and flavors, medium value industrial chemicals, and low value biofuels. The MIT and Wilson Center synthetic biology working groups have conducted a series of workshops on current and prospective materials production applications.

- One set of issues centers on the effectiveness of physical containment in limiting environmental effects. Regulators and firms suggest that agencies are sensitive to differences between the synthesis of high and medium value materials using yeast and bacteria in bioreactors and the synthesis of fuels using algae and cyanobacteria in lightly contained surface ponds, sluices and raceways.
- One set of issues centers on the effectiveness of biological containment measures in limiting environmental effects associated with inadvertent release. Methods of intrinsic containment have progressed from simple kill switches to Isaacs ab work on multiple nutrient dependency strategies to reduce fitness [14] and Church lab work on engineered genetic codes to limit horizontal gene transfer [9]. The Silver lab is developing self-monitoring safety systems incorporating integrated reporters to detect accumulating mutations that may compromise functionality of safeguards are now being developed. Regulators, firms, environmental scientists and civil society all noted the need for the development of protocols for testing and certifying methods of biological containment.
- One set of regulatory issues hinges on product characteristics. Public commentary focused largely on differences between industry and consumers/civil society on labelling and on the adequacy of current testing standards. An emerging issue centers on the synthesis of products such as opiates that may present public health and law enforcement problems yet fall within regulatory gaps, on the incorporation of technical features to limit illicit appeal and on the development of protocols for testing and certifying such safeguards. To prompt discussion on these issues in advance of development of robust and efficient strains, we published “Regulating Home Brew Opiates” in Nature in May 2015.[13]

<u>Question 3. How can Federal agencies improve their communication with consumers, industry, and other stakeholders regarding the authorities, practices, and bases for decision-making used to ensure the safety of the products of biotechnology</u>?

a. Federal agencies including EPA, FDA, USDA and security agencies have been willing and able to communicate effectively on jurisdiction, definitions and evidentiary thresholds, with us and with the firms, academic scientists, and non-governmental organizations with whom we work. This includes participation in a series of workshops on applications of synthetic biology, office visits, and presentations in academic and industrial forums.

b. Clarification of "bases used for decision-making" will require more than communication. In our experience, Federal agencies have clarified where possible but, even more significantly, have explicitly drawn attention to real areas of procedural and substantive ambiguity in order to prompt discussion. These areas are highlighted in the response to question 5 below.

c. While communication between agencies and stakeholders would be useful, differences in stakeholder perspectives are significant. As public comments suggest, firms seek greater clarity in the definition of areas of responsibility and streamlined regulatory processes with extensive white lists to bring product to market quickly and inexpensively, consumers seek credible information on product attributes and safety based on independent research and required labelling, and non-governmental organizations seek more stringent regulatory oversight based on independent research. Ironically, more communication between Federal agencies and stakeholders could underscore preexisting differences across industry, consumers and NGOs.

d. We suggest that communication strategies be augmented by strategies that promote engagement of firms, civil society, academics and concerned publics to discuss environmental, safety and security implications of specific applications of biotechnology, to identify associated uncertainty over implications, and to set research priorities to fill gaps. Such discussions are most effective at an earlier-than-typical phase of product development and licensing.

Question 4. Are there relevant data and information, including case studies, that can inform the update to the CF or the development of the long-term strategy regarding how to improve the transparency, coordination, predictability, and efficiency of the regulatory system for the products of biotechnology?

a. Workshops and discussions with regulators at offices overseeing regulation of biotechnology products have reinforced the findings of Snow [16] on substantial research needs regarding the safety, environmental and security implications of genetically engineered products.

- Research is needed on environmental implications, as summarized in "Creating a Research Agenda for the Ecological Implications of Synthetic Biology" Research Report, MIT Program on Emerging Technologies / Woodrow Wilson International Center, May 2014. [2]
- Research is needed on the effectiveness of technical measures intended to mitigate potential environmental, safety and security effects of synthetic biology. As noted above, technologists are redesigning bacteria to limit lateral gene flow and decrease fitness. Technologists working on gene drives are developing immunization drives to limit spread, developing reversal drives to partially undo undesired alterations, and introducing genetic instability as a design feature to decrease efficiency and localize effects. These measures need to be tested independently.

b. Case studies on successful examples of planned adaptation in regulation may be useful in developing biotechnology policies that promote innovation while taking account of broader environmental, health, safety and security effects. These are summarized in the extended discussion of long term issues and planned adaptation in the second part of this report.

c. Case studies on the origins and the effectiveness of voluntary measures to address environmental, health and safety implications of advanced biotechnologies may be useful in establishing the scope and intensity of formal rulemaking. Such voluntary measures include both the long standing case of transnational coordination by DNA synthesis firms to screen orders by sequence and by customer and the new case of development of a code of conduct by laboratories developing gene drives.[1]

Question 5. Are there specific issues that should be addressed in the update of the Coordinated Framework or in the long-term strategy in order to increase the transparency, coordination, predictability, and efficiency of the regulatory system for the products of biotechnology?

Note: Most of the examples below were provided by individuals working in Federal agencies.

a. EPA defines “genetically engineered” organisms as those to which DNA from a different taxonomic genus has been added. With new knowledge of genomics and new genetic engineering technologies, genetic changes with the potential substantially to effect an organism and its ecosystem can be made through deletion, duplication, or even rearrangement of genetic sequences within a given species or genus. Such changes now fall into a regulatory gap.

b. EPA defines “genetically engineered” as an organism produced through deliberate movement of DNA. Directed evolution has become more powerful through the use of new DNA sequencing technologies. Changes made through directed evolution now fall into a regulatory gap.

c. EPA treats instability of genetic constructs as undesirable. Some technical methods of intrinsic containment may deliberately build in instability to degrade the efficiency of constructs in order to localize potential effects. Ironically, regulations designed to protect the environment may preclude application of a potentially significant containment strategies.

d. Under a 2009 Guidance for Industry (GFI #187), FDA treats genetically engineered DNA constructs modified by rDNA methods intended to affect animals as veterinary medicines, with a requirement that such constructs be shown to be safe for the animal. Standards for veterinary medicines are difficult to reconcile with applications directed at suppressing invasive species or controlling vector borne diseases. To reduce ambiguity, the FDA is currently revising the 2009 Guidance, listing six classes of genetically engineered animals based on intended use and omitting modified insect disease vectors and invasive species. However, is still not clear whether gene drive modified organisms will be treated as the equivalent of conventionally genetically engineered animals. FDA also recognized “… that EPA may assert jurisdiction over certain GE animals as well. In addition, FDA is discussing with other agencies the best approach for oversight of GE insects. Future guidance may be developed to address them. FDA also will work with other relevant federal and state agencies should it receive a request for investigation or approval of a GE wildlife animal ultimately intended for release into the wild.”[5]

e. The Coordinated Framework has focused on the regulation of product rather than process. Genetic engineers are now producing organisms that differ fundamentally from comparators in nature, including mosquitoes incorporating gene drives that spread heritable malaria resistance rapidly or microbes whose genetic structure incorporates synthetic XDNA. These novel emerging products do not fit well within existing “product-based” regulations that assume essential equivalence of products produced using genetic engineering and conventionally produced analogs. The metrics to be used to compare a genetically engineered organism or product with non-engineered counterpart to determine equivalence are not clear.

PART TWO: LONG TERM STRATEGIES FOR RESPONSIBLE INNOVATION - PLANNED ADAPTATION

In July of 2015, the Biotechnology Working Group issued a three part memo on broader issues associated with updating biotechnology product regulation by July of 2016.[6] Biotechnology is now characterized by rapid change in foundational technologies, the development of better versions of existing products and processes, and the creation of unconventional applications. Our response to these developments is premised on the need for an overarching need for strategies of planned adaption as a response to associated uncertainty.

The original Coordinated Framework utilized predictions regarding the then-nascent biotechnology industry, and these should be revisited as the field develops. For example, the Coordinated Framework states that "By the time a genetically engineered product is ready for commercialization, it will have undergone substantial review and testing during the research phase, and thus, information regarding its safety should be available." Public comment divided on the definition of evidentiary thresholds to control use. Civil society favored invocation of the precautionary principle, with restrictions on use until safety is demonstrated. Firms favored use in the absence of clear evidence on harms.

By contrast, our recommendations focus on planned adaptation, with regulatory decisions based in part on research that generates knowledge on which initial authorizations of use may be based and in part of on systematic observation of applications-in-use that may be used to update and modify terms of use. Our thoughts on developing tools, procedures and schedules are framed in light of the need to reevaluate policies in light of emerging understandings of benefits, risks, and economic and societal context. To initiate discussion of appropriate arrangements in biotechnology, we recommend discussion of exemplary cases and cautionary tales from other areas to be used as a basis for design of a regulatory strategies in biotechnology. The brief examples below are described in greater length in Appendix B.

1. Lessons from Past Exemplary Cases

a. NTSB and FAA as an example of a two headed system with clear demarcation of an independent duty to gather and evaluate information and issue findings (NTSB) and to regulate by defining standards for airlines, aircraft manufacturers, air traffic control systems, and airports (FAA).

b. Netherlands Delta Management as an example of an explicitly adaptive system with publically funded scientific research directed at topics of direct relevance to agencies charged with responsibility for defining standards on dike construction, management of river flows, and zoning/land use.

c. US EPA CASAC / NAAQS as an example of an explicitly adaptive system with publically funded research on topics of relevance (PM2.5, health effects of methyl mercury) and regulatory scheduled review panels charged with assessing findings and incorporating findings into air quality standards.

d. EU BSE policy as an example of an explicitly adaptive system with systematic analysis of the incidence of BSE in cohorts of cattle, with feedback to relaxation of control measures found to be unnecessary.

e. EU European Medicines Agency implementation of adaptive pathways to licensing new drugs, with protocols limiting initial uses to patient populations with benefit/risk profiles that merit acceptance of uncertainty at the outset of use; with protocols governing acquisition and use of information on drugs in use; and with mechanisms for feeding back information to alter terms and conditions of use.[3]

2. Lessons from Past Cautionary Tales

a. NRC-NASA Shuttle management as an example of organizational resistance to adoption of adaptive risk management strategies because of fear of adverse findings and cost on viability of the program.

b. New Orleans and Army Corps of Engineers management of levees and dikes in the lower Mississippi area with weaknesses in systematic review and in updating of standards.

c. US FDA/FASEB/NIH research and regulation on transfats, with an NIH failure to incorporate early information on potential risks into research funding, with FASEB conducting facile and incomplete reviews of scientific literatures, and with long lags in FDA responses to data on health effects.

d. USDA BSE regulation with slow uptake of information on antibody selection in confirmatory IHC tests and with improper reliance on IHC tests that generated a false negative.
Note: McCray et al provide a review of US EHS cases where adaptive regulatory approaches were required, showing limited numbers of successful cases.[10] [11]

3. Planned Adaptation in Biotechnology Regulation

Analysis of the exemplary and cautionary cases provides a basis for highlighting three characteristics of effective planned adaptive regulatory systems for rapidly evolving biotechnologies. Policies should be proactive and adaptive, engaging with priors on risks/benefits and updating as understandings of risks and benefits evolve.

a. Setting Initial Conditions on Use: Both the phenomena being regulated and the effects of regulatory policies are not well understood upfront.
(1) There is need for targeted research to fill gaps in knowledge that are relevant to initial approvals of use. Some areas include research on technical mechanisms, on environmental, safety and security effects of applications including basic research on fitness, lateral gene flow and stability, and on the effectiveness of varieties of technical safeguards to limit environmental and security effects.
At present, the USDA BRAG program is explicitly designed to target research to improve scientific understandings in areas of concern to regulators of genetically modified organisms, with engagement with EPA, FDA as well as USDA in designating research priorities. We recommend that FDA and EPA as well as USDA have funding for research to inform decisionmaking in their designated areas of concern.
(2) The translation of priors on risks and benefits into authorization of use may be based, in part, on practices in pharmaceuticals, including FDA policies for accelerated approval and breakthrough product designation, EMA adaptive pathways pilots, and PMDA (Japan) conditional approvals on gene therapies and regenerative medicines.
At present, regulators of non-medical biotechnology do not take explicitly balance benefits, risks and uncertainty in initial approvals. The mechanical translation of adaptive pathways in medicines to broader biotechnology would not work, but we suggest that discussion of the suitability of elements of FDA, EMA and PMDA examples may usefully inform debate on revisions of the Coordinated Framework.

b. Observing/Sensing/Revealing: Parties differ in their interest in harvesting and sharing information needed to evaluate benefits/risks. Policies should create incentives and cut disincentives to reveal information needed for risk management (research funding, liability and IP law).
(1) There is need for systematic observation of applications in use to inform adjustments in policies. Some research topics worth considering include work on baselines against which to compare effects of applications and work on detection and traceability of genetically altered organisms, with this research of value in setting up systematic programs of surveillance of selected applications in use.
At present, NSF Molecular and Cellular Biology and USDA BRAG are potential sources of targeted support for research on these issues. We recommend that this initial pool of research on effects should be expanded to other agencies such as DARPA that are providing significant support for biotechnologies.
(2) There is need to address potential intellectual property rights issues as they affect the content and distribution of results of independent research. Debates over the effects of biotechnology have been hindered by suspicions of research that is controlled by institutions with interests in the outcomes of research. As Appendix C explains, these issues have been successfully addressed through both voluntary agreements with private industry and through public regulation.[15]
We commend USDA and biotechnology firms for reaching an ad hoc agreement on licensing independent research on genetically modified seed. We commend athe FDA, NIH and European Medicines Agency for structuring property rights in medical research, including clinical trials data, to protect the public interest

in improved understandings of safety, efficacy and effectiveness of drugs. We suggest that the USDA agreement on GM seed and the IPR arrangements on drug safety, efficacy and effectiveness should be used as a template for agreements in other biotechnology areas.

c. Credible knowledge assessment: Conflicts of interest, organizational inertia and prior beliefs typically bias observation and assessment. Policies should provide for credible and legitimate assessment of scientific and technical information under complexity, uncertainty and controversy. Models of how to evaluate scientific and technology knowledge in areas of controversy include:
(1) EPA and industry joint funding for the Health Effects Institute evaluation of the Harvard Six Cities study on PM 2.5, with feedback through CASAC to resetting PM standards;
(2) EPA/NIEHS convening of a conference on health effects of methyl mercury that brought together investigators with flatly opposed results and panels of disinterested experts on elements of research design to evaluate research designs; and then funded research using improved research designs that resolved the controversy;
(3) A National Research Council panel that evaluated technical studies on the impact and risks associated with the NIEDL BSL 4 laboratory; and
(4) American Physical Society Panel with a broad spectrum of technically informed stakeholders on the effectiveness of ballistic missile defense systems.
At present, a National Research Council Life Sciences Board ad hoc expert committee is in the midst of an appraisal of the state of research and governing regulations on gene drives and the NSABB is in the midst of a review of gain-of-function and dual use research of concern. Expansion of these mandates to other areas of controversy may be limited by the bandwidth of the NRC and NSABB. We recommend consideration of other models as noted above to supplement and augment the good work by these two institutions.

d. Fostering the Use of Information in Adaptation: Overcoming ordinary inertia and organizational interests can be the most difficult aspect of fostering adaptation and learning. The cases sketched in this section and other cases described in Appendix C provide a basis for several observations and recommendations.
(1) The deliberate separation of risk assessors from risk managers seems to be a design feature that works well. To take two examples, the NTSB operates independently from the powerful Department of Transportation, protecting its investigatory integrity, and the IETF is plainly built to ensure technical expertise, and operate at a distance from political sway and from self-interested market power. There appears to be some value in isolating the knowledge assessors from both public and private material interests until the risk assessment phase is settled by professional risk analysts.
(2) While recurring (often five-year) reviews are one mechanism for planning for future adaptations, it is not the only one that works. Event-based reviews are effective for airliner safety, and independent crash-testing has been important contributor to improved highway safety.
(3) Nongovernmental entities are central to several of the cases in Appendix C. Unilateral action by government is not the only way to ensure continuing progress. Non-governmental actors played a significant role in clinical care guidelines, the revision of fire safety standards, and the establishment and revision of internet protocols and standards.

PART THREE: APPENDICES

APPENDIX A: SUMMARY OF PUBLIC COMMENTS JANE MAUNSELL maunsell@mit.edu

Introduction

On October 6, 2015, the National Science and Technology Council released a Request for Information (RFI) to inform present and future changes to biotechnology regulation, including the ongoing update to the Coordinated Framework for the Regulation of Biotechnology, which is scheduled to be completed in July 2016. A total of 902 comments were submitted by the November 16, 2015, deadline. Commenters fell into three broad categories:

- consumer advocacy groups and members of the public commenting in support of tighter restrictions and requirements (88% of a 100-comment random sample),
- industry and science advocacy groups and researchers commenting in support of more efficient and permissive regulation (10%), and
- policy analysts identifying specific regulatory gaps and areas of improvement (2%).

This distribution provides only a rough first impression. Several comments were signed by many individuals or by representatives of large groups, while other comments were seemed copied and pasted, limiting the conclusions that can be drawn from raw frequency counts. This appendix outlines the set of proposals put forth by each group, with condensed summaries of salient comments.

Advocacy groups and members of the public

Consumer advocacy groups and organic farmers went beyond the scope of recommendations requested in the RFI, arguing for a fundamental restructuring of the Coordinated Framework that would include mandatory labeling, third party risk assessment, and other measures. Organic farming coalitions (e.g. the Northeast Organic Farming Associations of Massachusetts and New York) recommended compensation for GE crop contamination prevention measures taken by organic farmers. Several of these groups (e.g. the Center for Food Safety, Pesticide Action Network & Friends of the Earth) marshaled tens of thousands of members to sign petitions and submit their own comments. Indeed, as noted, comments by members of the public in favor of GE labeling, independent testing, and/or bans comprised the brunt of the 902 submissions. One consumer advocacy group proved an exception: the Center for Science in the Public Interest, a nutrition policy watchdog, expressed support for genetic engineering while arguing for filling regulatory gaps, clarifying roles, and conducting risk assessment to assuage public concern.

Summaries of selected comments (advocacy groups and members of the public)
Center for Food Safety, Pesticide Action Network, Friends of the Earth, other NGOs Institute mandatory, process-based regulation with independent testing of ecological and health risks. Risk assessment should follow the precautionary principle, prioritizing health and environmental safety over economic interests. Industry data should be made public, and manufacturers should be liable for contamination costs. Facilitate public participation at all stages of the regulatory process.
Northeast Organic Farming Association Implement mandatory labeling and third-party risk assessment and safety tests. USDA should disclose field trial locations and monitor for crop contamination to avoid rejection by more strictly regulated international markets.
Center for Science in the Public Interest

Make FDA inspection mandatory to assuage public concern. Fill regulatory gaps on gene editing technology and subject new regulation to regular, scheduled review.

Biotechnology firms and researchers

Individual firms and industry groups in regulated sectors were generally in favor of expanding exemptions and fast-tracking review (e.g. DuPont, TAXA, Revolution Bioengineering). Arguments by multinational firms and by agricultural associations (e.g. DuPont, Oxitec, and the National Grain and Feed Association and North American Export Grain Association) focused on the need for regulatory harmonization to facilitate trade and research. Several small firms and industry groups (e.g. the Biotechnology Industry Organization) argued that the costs, requirements and ambiguities of present regulation effectively bar entry of startups and specialty crops. Comments by academic biotechnology researchers (e.g. those submitted by the Cornell Alliance for Science) largely aligned with those of small biotechnology firms, focusing on regulatory barriers to market entry and research collaboration and the need for public outreach programs.

Summaries of selected comments (biotechnology firms and researchers)
DuPont Develop comprehensive US import policy and workable Low Level Presence policy for food, feed and seed. Expedite reviews and provide exemptions for familiar products.
National Grain and Feed Association & North American Export Grain Association Include export markets and market stakeholders in a broad trade-facilitation initiative.
Biotechnology Industry Organization Each agency should release its decision as soon as it is made, not wait for other agencies. OSTP should facilitate coordinated public outreach. Remove regulatory burdens when evidence supports it; approach to new tech should be "adaptable and science-based." See NIH GE research guidelines and USDA 2011 process improvement project as an example of adaptive regulation.
Oxitec Ltd Agencies should collaborate behind a "single window" for service of regulatory submissions. Manufacturers should publish safety data early in the process. Provide guidance on meeting interstate and international regulatory requirements. Case studies: the GE self-limiting mosquito strain was held back by expensive requirements and unpredictably timed review, whereas the Diamondback moth release was swift and efficient because agency responsibilities were defined and GE mosquito provided precedent.
TAXA (Glowing Plant Kickstarter campaign) Remove DNA from the TSCA review process. Eliminate NEPA. Only APHIS should regulate GE agrobacterium (not EPA and APHIS). EPA should create MCAN Tier III exemption for GE microbes. Encourage consumer GE products to increase public familiarity and trust with biotech. Fund risk assessment research to support creation of regulatory exemptions. Impose more postmarked requirements and lighten premarket requirements (Low Volume Exemption).

Revolution Bioengineering To determine regulatory authority, (1) assess risk that product will evolve beyond designed capacity and (2) identify possible interactions between GE product and environment in which it is kept. Change language for plant pest status—rather than having firms petition for "non-regulatable" status under USDA APHIS/BRS, give a more authoritative endorsement that clears up public skepticism. Also, narrow the definition of "plant pest" to GE plants that express proteins from a pest (exempt GE plants with untranslated genetic elements from pests, eg Ti plasmid).
Cornell Alliance for Science (compilation of comments by members belonging to the academic and industrial biotechnology communities) USDA FSIS should regulate transgenic animals; FDA should involve itself under CFSAN if at all. FDA-CVM should regulate GE animal models of human diseases. As case studies, note the benefits of virus resistant GE papaya and the regulatory and social barriers faced by Golden Rice and AquAdvantage. Regulation is too burdensome for small firms and researchers, thereby limiting biotechnology products to unpopular, not directly beneficial GE crops.

Policy analysts

Policy analysts, academic and otherwise, proposed frameworks for risk assessment and identified regulatory gaps and burdens (e.g. JCVI, ABSA, Wilson Center SynBio Project, Palmer, Fedoroff) and offered solutions. Others called for tighter regulation and monitoring (e.g. Cassuto & Levinson, Mellon).

Summaries of selected comments (policy analysts)
Policy analysts at J. Craig Venter Institute Fill regulatory gaps on gene editing. Clarify agency roles on field trials, animal gene editing, and dual-use products.
American Biological Safety Association USDA APHIS should regulate all GE plants and insects. FDA should strengthen substantial equivalence requirements and implement monitoring of field releases and trials. NIH guidelines should extend to all research (not just federally funded). Require manufacturers to publish Safety Data Sheet. Build website with information on regulations and agency authority (modeled after APHIS site on import permits). Each agency should develop safety and security training program for researchers and hobbyists. See JCVI 2014 report and Wilson Center Synthetic Biology Project. Require institutional review committees for academic research.
Woodrow Wilson Synthetic Biology Project Establish a centralized coordinating office. Conduct public outreach on synthetic biology. As case study, see Synthetic Biology Project crowdsourced inventory. Reserve 5% of federal synbio funding for risk assessment. Provide more resources to regulatory agencies, e.g. EPA and FDA.
Megan Palmer, Stanford University Establish standards for information sharing and harmonizing protocols across agencies. Provide public, clear, searchable information on regulatory frameworks, processes and precedents. Grant CBI status less freely. Build easily accessible and scalable communication interfaces

between regulators and practitioners, e.g. digital hotline and FAQs. Require structured reporting to assess regulatory system performance. Provide adequate funding to regulatory agencies and to research on policy and regulation.

Nina Fedoroff, Penn State University

Establish group of experts under NAS (with representation from each agency) to determine whether a product is exempt from review. Create and publish decision trees for developers to determine whether product is exempt/which agencies will regulate. See NIH Recombinant DNA Advisory Committee (RAC) as example of adaptive policy: policy was relaxed in response to mounting research demonstrating safety; also see NRC 1989 report "Field Testing GMOs: Framework for Decisions".

David Cassuto and Drew Levinson, Pace University School of Law

Group similar products into categories and appoint primary agency in charge of regulating each product area. USDA should impose monitoring requirements on all GE crops to study ecological risk. Designate USDA as primary regulator of all GE crops using PPA authority, with EPA and FDA performing supplementary review. Restrict EPA regulation of PIPs under FIFRA to simplify process.

Margaret Mellon, science policy consultant formerly at Union for Concerned Scientists

Use process-based triggers for case-by-case regulation. The range of traits in GE products on market is very small, so past safety evaluations do not really apply to more diverse technologies now in development.

APPENDIX B: HOW PLANNED ADAPTATION WORKS IN PRACTICE LAWRENCE MCCRAY lmccray@mit.edu

Starting by identifying policy arenas for which outcomes have, by objective measures, improved meaningfully over time, MIT researchers have attempted to discover the adaptive decision mechanisms that have helped reach those superior outcomes over time. The term "Planned Adaptation" is used here to signify such mechanisms. The cases below show how real institutions have managed to accommodate, and often to stimulate, new technologies in the furtherance of public safety and other national purposes. They demonstrate an ability to learn, over time, about causal factors that were not appreciated at the outset. The cases show a range of practical ways to make sure that policy can, over time, stay abreast of hard-to-anticipate changes in science, technology, and public opinion. One thing these cases have in common is a way of rewarding those who seek new knowledge relating to the benefits and risks of existing policies and standards. The cases also reflect a general willingness to acknowledge that the assumptions that underlay past policy decisions may need to be corrected in order to further improve decision outcomes.

Internet Standards: Government entities attempted to set standards for internet protocols over three decades ago, but could not reach timely agreement. Instead, technical leaders among internet users devised a system for deciding on rules of operation. That nongovernmental system, operated by the Internet Engineering Task Force, is marked by an open online discussion of newly-proposed standards, and the use of "rough consensus," rather than unanimity, to determine what new and revised standards are adopted. By the time a new standard is approved, it has normally been user-tested thoroughly by IETF specialists. With this setup, interconnectivity and growth have continued in the face of continual and major technology advances.

Guidelines for Cardiac Surgery: The first US science-based guidelines for cardiac health were written in the early 1980s. Since then, the guidelines have been repeatedly revised to reflect the latest science, and the latter versions show notable migration from the early versions. Survival rates and life expectancy continue to rise toward that of populations that have not experienced intervention to alleviate cardiac disease. The American College of Cardiology and the American Heart Association (ACC-AHA), two private groups of cardiac specialists, work jointly to provide this routine self-correction capability. For each guideline that is reassessed, the first step is a thorough review of recent outcome studies, including all known random clinical trials (RCTs) and meta-data reports for multiple RCT studies. Unlike many knowledge assessments, these guidelines do not restrict themselves to simple "do's and don'ts;" instead, they address all of the major clinical decisions that have to be made, and where the available research in less than conclusive, that fact is stated, thus throwing light on continuing research gaps. The ACC-AHA guidelines process reflects the move toward evidence-based medicine (EBM) in US health care. Formal study results are ranked higher than subjective expert opinion in assigning the strength of evidence ratings behind a particular action recommendation. The nongovernmental Institute of Medicine (IOM) has produced a series of influential reports on guideline-writing procedures across the whole field of U.S. health care.

National Transportation Safety Board (NTSB) and US Air Carrier Safety U.S. government's NTSB is often cited as a model of integrity and technical competence; it conducts intense (and strictly independent of U.S. regulatory programs) studies of the causes of actual airliner crashes in order to help assure that their causes are eliminated. With the expansion of commercial air travel, it is estimated that if 1960's levels of risk had not improved, we would see an airliner crash about every other day; instead, in recent years the US has seen no major fatal crashes at all . One unique practice in the NTSB program is that the Agency tracks the proportion of its recommendations that are actually implemented. Over 80% of them found to be adopted. Also unique to the NTSB program is the practice of publishing a "Most Wanted" list of subjects for new research -- and for renewed consideration of better safety solutions-- that NTSB finds to be generally underappreciated. One recent example is the problem of school-bus safety, symbolizing NTSB's credibility even beyond the boundaries of its original core mission.

EPA Regulation of Airborne Particulate Matter (PM) Under the Clean Air Act, the Environmental Protection Agency (EPA) is tasked to control risk from the emission of particulate matter (PM) and other airborne contaminants. The Agency is required to review its basic approach for each pollutant every five years in light of emerging knowledge. The agency's Clean Air Science Advisory Committee (CASAC), a group of outside experts, systematically reviews the latest scientific information on health and environmental risks, and its air program then issues a new regulation on PM. The upshot: originally the emission of "black smoke" was the main target of emissions controls for PM. In successive reviews, as more evidence came to light, the target was first changed to small (10 micron) airborne particles instead, and later still the target was further adjusted to reduce human exposure to 2.5 micron particles. The monetized health benefits of the resulting PM controls have been calculated to be in the range of $5 billion a year. Another interesting past feature of the PM program is that Congress allocated over a half-billion dollars for additional research on PM risk, and the independent National Academy of Science guided the setting of relative priorities for those research funds, based on potential health impact.

Highway Safety In the past 30 years, the U.S highway fatality risk per mile traveled has improved by about 60%. Many state and federal and private-sector factors contribute to this success. One of key factors the emergence of safer car designs. Here, planned adaptation takes the form of systematic new knowledge about survivability of different types of collisions. The Insurance Institute for Highway Safety (IIHS) has been a leader in this effort through its innovative crash-testing facility. It has been estimated that the fatality risk in a car with IIHS' "good" rating is a factor of four better than risk in a car with a "poor" rating. IIHS, organized in 1959 with funding by three major insurance companies, has over time introduced and implemented new varieties of crash tests in order to learn how car design affects occupant safety.

Delta Management in the Netherlands In 1953, within 20 days of a catastrophic flash flood of the south-west of the Netherlands, a commission was installed to lead the effort of to write the 'Deltaplan', which involved the constructions of dams and surge barriers to prevent reoccurrence. Only during the construction of the immense project, which lasted from 1958 till 1986, did the impact of the interventions on the ecosystem and society became visible. In September 2014 the Dutch parliament approved the follow-up 'Deltaprogramma 2015' that is projected to last till 2050. Having learned from the first program, the key feature now is planning flexibility explicitly termed 'adaptive delta management'. It goes far beyond flood defense and includes safeguarding fresh water supply, ecosystem management, the climate-proofing of the built environment, and maintenance of economic infrastructures. Alternative strategies are being prepared right from the start in order to be able to adjust the program to changing conditions, e.g. in climate and sea level rise, as they occur. Adaptive delta management builds on coordinated decision making by a large number of ministries and agencies, research institutes, national and local population, and industry and commerce.

Urban Fire Safety Since the late 1970s, the number of building fires in the U.S. has fallen by more than 60%, and the number of fire deaths in homes has declined by over 50%. Today, a fire department's emergency responses are much more likely to supply medical aid (which account for 64% of all calls) than either fires (4%) or false alarms (8%). The reasons for this steady long-term improvement are not clear, and are probably multifactorial. Representatives of the National Fire Protection Association (NFTA) cite the introduction of technologies including fire detectors and automatic sprinklers. The contribution of insurance entities, and their loss data, may prove to be a significant part of this story.

APPENDIX D: PATENTS AND ACCESS FOR RESEARCH

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A Proposal for Regulating Biotechnology in a Manner that Promotes Openness and Sharing

The Request: On July 2, 2015, the Executive Office of the President issued a Memorandum, titled "Modernizing the Regulatory Framework for Biotechnology Products," that called on officials of the Food and Drug Administration (FDA), the Environmental Protection Agency (EPA), and the United States Department of Agriculture (USDA) to: (1) convene a working group for updating the Coordinated Framework for the Regulation of Biotechnology; and (2) develop a long-term strategy to ensure that the regulatory systems is equipped to assess and address the health, environmental, and security concerns associated with emerging biotechnologies, while reducing regulatory burdens and increasing transparency and public confidence.

While the mandate for the first objective was relatively limited, it specifically requested that the updates to the Coordinated Framework clarify how agencies should address problems that cross agency boundaries. The mandate for the second objective requested that the strategic plan support "the science that informs regulatory activities with regard to the assessment of biotechnology products," and ensure that regulatory evaluations are "risk-based and grounded in the best available science." It also asked for proposed changes in regulations or public policy that would improve the ability of regulators to quickly assess potential impacts and risks associated with emerging biotechnologies while ensuring transparency and predictability.

This proposal addresses these requests by describing the ways in which biotechnology patents can be used to interfere with the research needed to inform public policy, and proposing legislative and regulatory changes that will promote the openness and sharing needed to ensure that the regulatory framework responds efficiently and appropriately to emerging biotechnologies.

Patents and Access Problems: For those outside the domain of patent law specialists, it may seem strange to consider patent rights in connection with proposed revisions to the biotechnology regulatory framework. We have become accustomed, as a society, to thinking of patents only as a tool that provides important incentive for firms to invest in the research and development that leads to new and better technologies. Unfortunately, this widely shared perspective emphasizes important benefits while ignoring significant risks associated with each patent grant, risks that escalate when the patent holder also adopts restrictive (albeit, perfectly legal) licensing practices. Though these risks are myriad and affect competition and technological progress in many ways, the most important risk for regulators is the risk that an individual or firm holding a patent on a new biotechnology will use the patent to suppress or manipulate the research needed to inform public policies addressing the health, environmental, and security consequences of that technology.

The following case studies drawn from three domains of genetic research illustrate some of the risks that patent rights can create for other scientists, and emphasize a few key points that regulators should consider when updating the Coordinated Framework and developing a strategic plan for biotechnology innovation. While the third case study is the most germane, the other two draw attention to significant risks that are often overlooked.

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1 OncoMouse – In 1988, the United States Patent and Trademark Office (PTO) issued a patent to Harvard University for its invention of the OncoMouse, a genetically modified mouse predisposed to developing cancer. Under an exclusive license from Harvard, DuPont refused to license the OncoMouse to cancer researchers unless they agreed to terms that prohibited sharing or breeding of the mice, and required annual disclosures of research results and a grant-back to DuPont of all inventions (including cancer therapies) developed through use of the mice. Eleven years after the patent first issued and after four years of negotiations, the National Institutes of Health reached a Memorandum of Understanding with DuPont that was intended to facilitate sharing with universities and non-profit entities, but even this agreement did not completely resolve the controversy.[2]

Key takeaway: Negotiating ad hoc solutions to patent-based access problems can consume enormous amounts of regulatory resources, and even then, the effort may not succeed. Regulators should establish firm codes of conduct that promote norms of openness and sharing—especially when it comes to research for assessing the health, environmental, and security consequences of emerging technologies—long *before* a controversy arises.

2 BRCA Genes – In the late 1990s, the PTO granted to Myriad Genetics a series of patents covering the isolated DNA sequences for genetic mutations that were highly correlated with the risk of developing breast or ovarian cancer (BRCA genes). Through litigation threats and cesist and desist letter, Myriad solidified its position in the market as the only provider of diagnostic tests to determine if a person carried such a mutation until the Supreme Court held, in 2013, that isolated DNA sequences are not eligible for patenting. Before the Supreme Court decision, Myriad also took the position that clinical researchers working on alternative causes of breast and ovarian cancer violated its patents if they attempted to identify a BRCA mutation solely for purposes of ruling out BRCA causation.[3]

Key takeaway: Patents on biological materials can enable the patent holder to block, tax, or control research on alternative causal mechanisms—the central component of any useful scientific assessment for public policy. While the Supreme Court's decision provided much needed relief in the case of isolated DNA sequences, it remains unclear how the decision will apply to patents covering other non-DNA biotechnologies, including biological receptors or markers.

3 GM Seeds and Plants – In a public letter to the Environmental Protection Agency in 2009, Cornell University entomologist Elson Shields and about two dozen other scientists revealed that the major agricultural technology companies in the United States were licensing genetically modified seeds and crops to the public on terms that prohibited research on health and environmental consequences, and then selectively permitting such research to move forward only with those scientists who were "friendly" to industry. Once the problems were publicly revealed, the American Seed Trade Association entered into an agreement to facilitate more open sharing, though Shields claimed that he and his fellow scientists had endured intimidation and attempted to work around the access problems for more than 10 years by the time he wrote the letter.[4]

Key takeaway: The access problems engendered by patents and aggressive licensing do not only impact those conducting research with commercial applications, but also affect those conducting research to

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[2] Sasha Blaug, Colleen Chien, and Michael J. Shuster, *Managing innovation: university-industry partnerships and the licensing of the Harvard mouse*, 22 NATURE BIOTECHNOLOGY 761 (2004); Rebecca S. Eisenberg, *Noncompliance, Nonenforcement, Nonproblem? Rethinking the Anticommons in Biomedical Research*, 45 HOUS. L. REV. 1059, 1072-75 (2008).

[3] *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S.Ct. 2107 (2013); Rochelle Dreyfuss, *Protecting the Public Domain of Science: Has the Time for an Experimental Use Defense Arrived?*, 46 ARIZ. L. REV. 457, 459 (2004).

[4] *Do Seed Companies Control GM Crop Research?*, SCI. AM. (Aug. 1, 2009), http://www.scientificamerican.com/article/do-seed-companies-control-gm-crop-research/ [https://perma.cc/9XZH-HKLC]; Bruce Stutz, *Companies Put Restrictions On Research Into GM Crops*, YALE ENV'T 360 (May 13, 2010), http://e360.yale.edu/feature/companies_put_restrictions_on_research_into_gm_crops/2273/ [https://perma.cc/XBG2-DW3V].

inform public policy. Even if ad hoc solutions are achieved and scientific evaluation moves forward, the secrecy and controversy surrounding the process may undermine public confidence in the results.

As these three examples illustrate, if a patent holder takes an aggressive licensing position, it can exert substantial power over the course of subsequent scientific research, even if that research is directed at evaluating a new technology or assessing its potential consequences for human health, the environment, or national security. Not all patent holders adopt aggressive licensing postures, and not all technological settings are prone to the same potential for abuse. At the same time, waiting for controversy to arise before regulators intervene may impede the success of the ultimate intervention and undermine public confidence, and biotechnologies seem especially prone to these types of access problems.

Proposed Legislative and Regulatory Changes In the 1980s, when most of the major pieces of modern patent legislation were passed and the Coordinated Framework was first created, most economists and policy-makers who analyzed the patent system relied on studies that modeled the innovative process in a "stove-piped" fashion, with financial and human capital as inputs and patents as outputs. In the early 1990s, a handful of economists and legal scholars noticed that these models did not accurately capture the dynamics of the modern "cumulative" research environment, where patents are both inputs to and outputs from the research process.[5] That realization has enormous implications for policymakers, as the power inherent in the patent grant undeniably confers the power to tax or stifle subsequent research on or with the patented invention.

Unfortunately, patent policymakers and those who regulate technological development have been slow to incorporate these insights into existing legal frameworks. The two proposals described below are premised on the belief that patents do create strong investment incentives and confer important benefits on society, but they also create a significant risk of abuse in the absence of rules or regulations that promote openness and shield those undertaking exploratory research from the risk of liability for patent infringement.

Recommendation 1 -- Codify a Robust Research Exemption: To ensure that regulators are poised to assess and address the health, environmental, and security risks of emerging biotechnologies, it is essential that all regulatory agencies coalesce in support of legislation to codify, once and for all, a broad research exemption that would immunize all acts of research or experimentation on or with a patented invention from infringement liability.

As Table 1 at the end of this proposal shows, a significant number of federal advisory committees since the middle of the 1990s have recommended codifying a research exemption in United States patent law in one form or another. Some committees understandably limited the request to the technological space analyzed in the report (genes, for example), while others proposed to narrow the scope of the exemption based on certain institutional or technological distinctions. Such distinctions, which legal scholars also frequently invoke, include those between public and private entities; between basic and applied research; between research and later-stage "development" or commercialization; between technologies that are sold in normal consumer markets and "research tools" that are only used for scientific research; and between research performed "on" as opposed to "with" a patented invention.

Though the scholars that have argued in favor of these distinctions have done so out of a laudable desire to narrowly tailor the proposed policies, all the distinctions they have drawn are ultimately unworkable, and there is no legal or economic basis for using them to narrow the scope of the research exemption. Setting the plight of individual firms aside, a patent law designed to maximize the benefit to the economy and society as a whole should freely grant patent protection to the broadest possible range

[5] Robert P. Merges & Richard R. Nelson, *On the Complex Economics of Patent Scope*, 90 COLUM. L. REV. 839, 842–44 (1990); Suzanne Scotchmer, *Standing on the Shoulder of Giants: Cumulative Research and the Patent Law*, 5 J. ECON. PERSP. 29 (Winter 1991).

of subject matter subject to an equally broad exemption protecting virtually all forms of research or experimentation on or with the patented invention, regardless of institutional setting or purpose, so long as there is no revenue-generating sale or offer for sale.

Over the last 30 years, the law regarding research exemptions has developed in a complex and ad hoc fashion. Currently, a common law research exemption and a statutory exemption in the Plant Variety Protection Act (PVPA) exist on the books but have been significantly narrowed in judicial opinions, while a broad statutory exemption for research on drug and veterinary products has received significant judicial support. At the same time, the courts have tried to pursue some of the same results that should be achieved through a research exemption through other doctrinal means, like state sovereign immunity or subject matter eligibility.[6] Unfortunately, this means that existing law treats state universities and agencies differently from all other public and private institutions, and instead of rules that protect certain *conduct*, we have rules that protect experimentation within certain technological *categories* (depending on the shifting boundaries of the patent eligibility doctrine).

Codifying a robust research exemption would minimize regulatory burdens by obviating the need for regulatory intervention regarding abusive licensing practices, or providing a firm legal basis to define the goal of regulatory intervention when controversies arise. It would help ensure that regulators are armed with the highest quality scientific analysis available when setting public policy or promulgating rules by protecting those who undertake such research from the risk of infringement liability, while also giving those researchers a firm legal basis for demanding access to technologies for evaluation. And it would normalize United States law by creating a clear code of conduct across all institutional and technological settings.

Recommendation 2: Coordinate Regulations with Grant-Providers to Support Openness and Sharing

Though the FDA, the EPA, and the USDA do not predominately function as grant-providers in their everyday operations, they do have the ability and authority to regulate in a fashion that is consistent with the policies of grant-providing institutions like the National Science Foundation and the National Institutes of Health (NIH). Generally speaking, the National Institutes of Health have led the way in developing model regulations governing patenting decisions, licensing practices, and the terms of Material Transfer Agreements (or MTAs).[7] Policies embodied in a forward-looking strategic plan for regulating biotechnology should be integrated and coordinated with those policies of grant-making institutions that attempt to facilitate the free exchange of information and ideas. At the very least, all three agencies should consider creating a channel for those who allege that a firm seeking regulatory approval has refused access or otherwise interfered with evaluation of a technology to formally (and perhaps anonymously) lodge a short complaint, and a process for evaluating such complaints in connection with any regulatory decisions.

[6] For a political analysis of these developments, see Nicholas Short, *The Political Economy of the Research Exemption in American Patent Law*, --- FORDHAM INTELL. PROP., MEDIA, & ENTERTAINMENT L. J. --- (2016, forthcoming). For the statutory drug exemption, see 35 U.S.C. 271(e); *Merck KGaA v. Integra Lifesciences I, Ltd.*, 545 U.S. 193, 202 (2005) (holding that the exemption applies to exploratory research and early-stage experimentation); Congressional Budget Office, *Research and Development in the Pharmaceutical Industry*, Pub. No. 2589, at 7-8 (October 2006) (estimating somewhere between a three- and seven-old increase in drug research investment over a time frame in which a research exemption was in place).

[7] See National Research Council, *Reaping the Benefits of Genomic and Proteomic Research* (2006) at 137-8.

TABLE 1: REPORTS BY FEDERAL ADVISORY GROUPS

Organization Committees	Year	*Title* Recommendation
Department of Health and Human Services Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS)	2010	*Gene Patents and Licensing Practices and Their Impact on Patient Access to Genetic Tests* Proposing codification of a research exemption applicable to gene patents.
National Research Council Committee on Science, Security and Prosperity; Committee on Scientific Communication and National Security Development, Security, and Cooperation; Policy and Global Affairs	2009	*Beyond "Fortress America": National Security Controls on Science and Technology in a Globalized World* Proposing, as an action item, that the Fundamental Research Exemption of National Security Decision Directive 189 (NSDD-189) be maintained and properly implemented in order to "assure the scientific and technological competitiveness of the United States."
National Research Council Committee on Intellectual Property Rights in Genomic and Protein Research and Innovation; Board on Science, Technology, and Economic Policy; Committee on Science, Technology, and Law; Policy and Global Affairs	2006	*Reaping the Benefits of Genomic and Proteomic Research* Recommending a limited research exemption protection research "on" but not "with" a patented invention, similar to that which exists in several European countries.
Institute of Medicine Committee on Advances in Technology and the Prevention of their Application to Next Generation Biowarfare Threats; Development, Security, and Cooperation Policy and Global Affairs Division; Board on Global Health	2006	*Globalization, Biosecurity, and the Future of the Life Sciences* In a letter to the Secretary of Commerce, noting that proposed revisions to export control regulations "could eviscerate the NSDD-189, and indicating that the National Academies "favor a crisply defined regulatory 'safe harbor' for fundamental research, so that universities can have confidence that activities within the 'safe harbor' are in compliance, and so that the vital importance to national security of open fundamental research is re-affirmed as a matter of national policy."
National Research Council Committee on Intellectual Property Rights in the Knowledge-Based Economy; Board on Science, Technology, and Economic Policy; Policy and Global Affairs Division	2004	*A Patent System for the 21st Century* Recommending that Congress consider legislation to codify a research exemption or, if political progress is slow, that the Office of Management and Budget and the federal agencies undertake administrative action to preserve access to the public research "commons."
Institute of Medicine Committee on Large-Scale Science and Cancer Research, National Cancer Policy Board	2003	*Large-Scale Biomedical Science: Exploring Strategies for Future Research* Recommending that the National Institutes of Health and the National Cancer Institute should "use their leverage

and National Research Council Division of Earth and Life Studies		and resources to promote the free and open exchange of scientific knowledge and information, and to help minimize the time and expense of technology transfer," and "promote licensing practices that facilitate broad access to research tools by issuing licensing guidelines for NIH-funded discoveries."
National Research Council Commission on Life Sciences	1999	*Finding the Path: Issues of Access to Research Resources* Concluding that "[n]early every field of biology is experiencing problems in the transfer of research resources among members of its research community" and that the dissemination of research resources "often gets bogged down in issues of ownership, equity, availability, cost, appropriate use, value, and maintenance."
National Research Council	1996	*Intellectual Property Rights and Plant Biotechnology* Noting that several members of the forum panel called for a research exemption.
National Research Council	1996	*Intellectual Property Rights and Research Tools in Molecular Biology* Expressing concern that a broad research exemption might inhibit incentives for the narrow subset of technologies that are only useful as an input to further research.
Institute of Medicine Committee on Resource Sharing in Biomedical Research, Division of Health Sciences Policy	1996	*Resource Sharing in Biomedical Research* Concluding that funding agencies and regulators play an essential role in successful sharing efforts, and calling for further inquiry as to how to protect the research exemption.

TABLE 1: REPORTS BY FEDERAL ADVISORY COMMITTEES
This table presents the author, year of publication, title, and relevant conclusion or finding of ten separate reports by federal advisory committees, over the last twenty years, that have investigated the impact of patents or other impediments to norms of openness and sharing on biotechnology research.

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