REPORT TO THE PRESIDENT AND CONGRESS ON THE FIFTH ASSESSMENT OF THE NATIONAL NANOTECHNOLOGY INITIATIVE

Executive Office of the President
President's Council of Advisors on
Science and Technology

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PRESIDENT'S COUNCIL OF ADVISORS ON SCIENCE AND TECHNOLOGY
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President Barack Obama
The White House
Washington, DC 20502

Dear Mr. President,

We are pleased to present to you the *Report to the President and Congress on the Fifth Assessment of the National Nanotechnology Initiative*, a review by the President's Council of Advisors on Science and Technology (PCAST). This report fulfills PCAST's responsibilities under the 21st Century Nanotechnology Research and Development Act (Public Law 108-153) and Executive Order 13349 to provide periodic updates to Congress.

The Federal Government has invested over $20 billion in nanotechnology research in the past 13 years, leading to great success in creating the building blocks of nanoscience. In this review, PCAST determined that the National Nanotechnology Initiative (NNI) has reached a turning point. The vision of NNI is a future in which the ability to understand and control matter at the nanoscale leads to a revolution in technology and industry that benefits society. To realize this vision, PCAST recommends that the Federal Government transition its activities toward facilitating commercialization by directing the formulation of specific nanotechnology Grand Challenges. The Grand Challenges framework—a partnership between the public and private sectors—can drive scientific advances to revolutionary commercialized products.

PCAST recommends a process to identify the Grand Challenges and several program-management changes to ensure their success. New Federal activities can catalyze academic entrepreneurs and industry to come together and the manufacturing sector to consider producing these promising new technologies. The United States has made good progress in addressing environmental, health, and safety (EH&S) issues associated with nanotechnology, and the evaluation found that work on EH&S must continue so that new technologies are adopted with the full trust of the public.

Continued support of fundamental research in nanoscience is also critical. New technologies a decade from now will be built on exploration and discovery today. With strong awareness of how other countries are competing for the most talented scientists and engineers, PCAST recommends ways to attract and keep these individuals in the United States and sustain this country's advanced nanotechnology research infrastructure.

The transition toward commercialization can have implications for drug delivery, energy technology, smart sensors, clean water, quantum computing, and more. The United States can continue to lead in research and development, and the time is now to ensure the Nation will lead in the commercialization of nanotechnology, as well. PCAST thanks you for your interest in this important domain of American leadership in science, technology, and innovation.

Best regards,

John P. Holdren

John P. Holdren
Co-chair, PCAST

Eric S Lander

Eric S. Lander
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Executive Summary

The National Nanotechnology Initiative (NNI) is a crosscutting national vision for nanotechnology development in the United States. The Federal effort in nanotechnology coordinates U.S. investment in research and development (R&D) in nanoscale science, engineering, technology, and related activities across the U.S. Government. In FY2014, even though five agencies garnered 93 percent of the Federal spending in nanotechnology R&D, 27 agency units from 20 top-level Federal entities participated in nanotechnology activities. The 21st Century Nanotechnology Research and Development Act of 2003 calls for a National Nanotechnology Advisory Panel to review the NNI periodically [3]. Designated in 2004 to be that panel, the President's Council of Advisors on Science and Technology (PCAST) has reviewed the NNI five times, and this report is the third of this Administration's PCAST.

In the course of our overall assessment, we first reviewed the responses to the recommendations in the PCAST 2012 NNI review [4]. One core recommendation was to increase funding to the Nanotechnology Signature Initiatives (NSIs). In contrast, we find that overall funding for the NSIs has remained flat, and we further find that funding for Solar Energy Collection and Conversion, Nanomanufacturing, and Nanoelectronics – the first three NSIs, which were created in 2011 – actually decreased; the proposed FY2015 NSI budget is down 28 percent from the FY2011 budget. The 2013 National Research Council Committee on the Triennial Review of the NNI examined the practices, agency collaborations, and progress of the 2011 NSIs and determined that only a few of the characteristics the Government Accountability Office (GAO) has published as best practices – purpose, scope, and methods; problem definition; and risk assessment – were addressed adequately; most of the initiatives only partially addressed other key characteristics such as resources, investments, integration, and implementation [5, 6]. The decrease in budget for the original NSIs and the NRC review imply that while NSIs may be good vehicles for identifying common areas in which participating agencies are investing, they are not serving as an effective vehicle for achieving the long-term vision of the NNI. Other 2012 recommendations included creating a standing Nanotechnology Steering Committee of outside experts and developing and tracking the metrics needed to quantify the Federal nanotechnology portfolio. Little activity has occurred that is responsive to these two important recommendations.

The Federal Government has proposed $1.537 billion of nanotechnology funding in FY2015, an amount roughly comparable to FY2014 funding. We find that the sustained level of funding to date has delivered significant scientific and technological progress and that continued innovation calls for a healthy research effort to continue. But international competition for leadership in nanotechnology has increased on many fronts, as evidenced by a 2014 GAO report stating that while the United States remains preeminent in nanotechnology research, it has fallen behind other countries in developing the necessary infrastructure and workforce required to manufacture many nano-based products [7].

Our work in this PCAST 2014 review is based on the premise that the nanotechnology field is at a critical transition point and has entered its second era, which we call NNI 2.0. This next technological generation will see the evolution from nanoscale components to interdisciplinary nano-systems and the movement from a foundational research-based initiative to one that also provides the necessary focus to ensure rapid commercialization of nanotechnology [8].

It is important to recognize that while Federal agencies prioritize nanotechnology as an area for investment and activity, the entire Federal activity is not a single, centrally-funded program with separate, line-item budget authority. The added value of the first phase of NNI in creating collaborations among various agencies is no longer enough given international competition and the maturation of the field. The primary conclusion of our 2014 PCAST review is that the United States will only be able to claim the rewards that come from investing in nanotechnology research and sustaining an overarching Federal initiative if the Federal interagency process, the Office of Science and Technology Policy (OSTP), and the agencies themselves transition their nanotechnology programmatic efforts beyond supporting and reporting on basic and applied research and toward building program, coordination, and leadership frameworks for translating the technologies into commercial products.

This report makes a number of recommendations in areas related to programmatic focus, program management, commercialization, measurements, and attention to environmental, health, and safety (EHS) concerns. Details are provided in the sections that follow. Here we note the three most important recommendations that we believe are necessary to bring about the focus and direction needed for NNI 2.0 to be successful.

1. While certain elements of the current Nanotechnology Signature Initiatives framework should be maintained, the primary active program-management structure should be driven by the Federal and OSTP commitment to the concept of nanotechnology Grand Challenges.
2. We reiterate the need for an ongoing, separate standing committee of cross-sector nanotechnology experts that advises, but does not evaluate, the nanotechnology activities of the U.S. Government. We also iterate the need for a functional interagency process via the National Science and Technology Council, the Committee on Technology, and the Nanoscale Science, Engineering, and Technology (NSET) Subcommittee that is able to make cross-agency funding priorities when needed to address nanotechnology Grand Challenges [9].
3. We reiterate the need to assess Federal nanotechnology research and commercialization funding through a more formal system of metrics.

Implementing the Grand-Challenges framework, continuing to support vital discovery and exploratory research, and continuing an active, collaborative, and competitive international engagement will ensure that NNI 2.0 is a successful and vibrant Initiative.

This report describes in detail the rationale and characteristics of Grand Challenges, how they differ from Signature Initiatives, and provides illustrative examples that could be suitable for NNI 2.0. Because the Grand-Challenges process outlines specific technical goals and the active management needed to accomplish them, that process, which has been used in a number of OSTP-led scientific and technology programs, can provide the necessary framework for commercialization opportunities to mature. Illustrative Grand Challenges for nanotechnology include nano-enabled desalination of seawater to solve the emerging water crisis, reducing global greenhouse emissions with nano-enabled solid-state refrigeration, creating a forefront of manufacturing through nano-3D printing, and developing a nanoscale therapeutic for at least one major cancer.

In addition to the three primary recommendations noted above (Grand Challenges, an active advisory committee, and development of processes to measure the effectiveness of the Initiative), this review makes additional recommendations aimed at enhancing the transition to NNI 2.0. We note that while these measures are meant to support the enhancement of nanotechnology investments that foster commercial transition of maturing nanotechnologies, this focus on commercialization should not preclude the Federal Government from investing in and coordinating discovery and exploratory research, which is the bedrock on which commercial technology builds. We recommend that the National Science Foundation (NSF) expand the NSF Innovation Corps to include a specific focus on entrepreneurship in the nanotechnology area; that with the guidance and support of NSET, the Federal agencies define potential Institutes for Manufacturing Innovation dedicated to nanoscience and nanotechnology as part of the National Network for Manufacturing Innovation program; and that Federal agencies extend or create programs that substantially support single investigators for five years to pursue creative, high-risk research in nanoscience and nanotechnology.

We commend NSET for its successful coordination of nanotechnology R&D activities within the Federal Government, and we specifically highlight the NSET Nanotechnology Environment and Health Implications (NEHI) Working Group. NEHI remains an active and collaborative cross-agency forum that released on June 26, 2014 a review of NNI EHS research activities, accomplishments, and collaborations entitled, “Progress Review on the Coordinated Implementation of the NNI 2011 EHS Research Strategy.” We recommend that NSET continue on this path and support further the development of a multidisciplinary nanotechnology EHS ecosystem that will expedite safety assessment, decision making, and commercialization. A fundamental Government role in attending to EHS issues will endure regardless of the shape of the Initiative.

The National Nanotechnology Initiative has been a truly successful venture for the past 13 years, and the nanotechnology community has built strong foundations for the future. NNI 2.0 will require an actively-led ecosystem that integrates the efforts of academic, industrial, Federal, and philanthropic partners and more to bring the vision of the NNI into commercial reality. Much of the analysis and many of the recommendations in this report are not new. With the enhanced focus on the transition to commercialization, the implementation of the Grand-Challenges framework, and more aggressive leadership, we believe the recommendations contained herein will lead to a successful NNI 2.0 for the coming decade. We believe the implementation of these recommendations to be critical to that success. If another two years passes without these kinds of changes, we believe the value of a centrally-reported NNI will be substantially decreased. The next PCAST review will most certainly focus on the success of this implementation.

Summary of Recommendations

Grand Challenges for NNI 2.0 Recommendations

Recommendation 1. Establishing Grand Challenges is an effective means for focusing and amplifying the impact of Federal nanotechnology activities. The Nanoscale Science, Engineering, and Technology Subcommittee and the Office of Science and Technology Policy should identify a list of candidate nanotechnology Grand Challenges that address significant societal needs. At least one Grand Challenge should contain program elements aimed at manufacturing challenges specific to that focus area.

Recommendation 2. The Nanoscale Science, Engineering, and Technology Subcommittee and the Office of Science and Technology Policy should create and execute a process to engage research, development, and industrial stakeholders in the identification and selection of Grand Challenges on an ongoing basis.

Recommendation 3. Federal agencies, with support from the Office of Science and Technology Policy, should offer implementation tools like innovation prizes and public-private partnerships to encourage researchers to reach critical milestones on the path to completing Grand Challenges.

Program Management Recommendations

Recommendation 4. The Nanoscale Science, Engineering, and Technology Subcommittee should continue to be co-chaired by the Assistant Director, Nanotechnology in the Office of Science and Technology Policy and a representative of one of the participating agencies on a rotating basis. The Assistant Director should ensure that a leader for each active Grand Challenge also participates in a leadership role in the subcommittee. The Nanoscale Science, Engineering, and Technology Subcommittee should use Grand Challenges as the primary vehicle for actively managing the Federal nanotechnology activities toward directed outcomes.

Recommendation 5. PCAST should continue to carry out the Congressionally required periodic review of the NNI. Congress should align this review and the triennial National Research Council reviews to the same concurrent three-year time interval to reduce the burden on the Initiative. The Office of Science and Technology Policy, with the support of the National Nanotechnology Coordinating Office, should create and administer a separate standing committee of cross-sector nanotechnology experts that provides guidance, but does not evaluate, the NNI.

Recommendation 6. The Nanoscale Science, Engineering, and Technology Subcommittee, with the Department of Commerce, should execute a process to establish a common set of evaluation metrics to quantify and report the impact on workforce, productivity, and scientific knowledge in nanotechnology for all new research and commercialization programs beginning in FY2016.

Commercialization Recommendations

Recommendation 7. The Nanoscale Science, Engineering, and Technology Subcommittee should work with the Federal agencies to define potential Manufacturing Innovation Institutes dedicated to nanoscience and nanotechnology as part of the National Network for Manufacturing Innovation program.

Recommendation 8. The National Science Foundation (NSF), in consultation with the Nanoscale Science, Engineering, and Technology Subcommittee (NSET), should expand the NSF Innovation Corps to include a specific focus on entrepreneurship in the nanotechnology area, and NSET, the National Institutes of Health, and the Department of Energy should leverage this program concept to make it available to a broad range of scientists working in nanoscience and technology.

Recommendation 9. The National Nanotechnology Coordinating Office and the Department of Commerce should establish an annual nano-focused economic-development forum designed to bring together academic researchers, the venture capital community, biotechnology, and other industry in a format that enhances the possibility to create business partnerships.

Research Enterprise Recommendations

Recommendation 10. Recognizing growing international funding competition that is attracting US-based talent to go abroad, NNI agencies should substantially support the best single investigators to pursue creative, high-risk research. In particular, the National Science Foundation, Department of Energy, Department of Defense, and National Institutes of Health should coordinate to ensure that at least five new National Security Science and Engineering Faculty Fellowship (NSSEFF)-style senior-investigator grants in nanoscience and nanotechnology are funded per year.

Recommendation 11. The National Science Foundation, National Institutes of Health, Department of Energy, Department of Defense, and the National Institute of Standards and Technology should strongly support nanoscale research centers and infrastructure networks to ensure the effective training of a new generation of transdisciplinary scientists and engineers, in particular by strongly supporting the Next-Generation National Nanotechnology Infrastructure Network.

Environmental, Health, and Safety Recommendations

Recommendation 12. The Nanoscale Science, Engineering, and Technology Subcommittee should continue to support the development of a multidisciplinary nanotechnology environmental, health, and safety ecosystem that promotes non-animal based (alternative) test strategies for safety assessment and multi-stakeholder participation in regulatory decision-making and safe implementation to facilitate market access of nanomaterials and nanotechnology-enabled products.

Chapter 1. Introduction & Overview

Introduction

This report conveys the fifth review of the National Nanotechnology Initiative by the President's Council of Advisors on Science and Technology (PCAST). To execute the review, we formed an 11-person working group of outside advisors who informed the evaluation.

PCAST strongly supports fundamental research in nanoscience and across the physical and natural sciences. We found that Federal investment in nanotechnology has built a strong scientific foundation for creating, studying, and understanding new classes of nanoscale building blocks. We expect fundamental nanoscience research to continue uncovering new insights that bridge understanding between the atomic scale and the macroscopic scale. But the Federal Government's intense interest in nanoscale research and development is not driven by increasing fundamental knowledge in nanoscale science for its own sake – a goal deeply appreciated by this Council – but instead aims to create new technologies that improve the lives of Americans and people everywhere. "There's plenty of room at the bottom," said physicist Richard Feynman about technology opportunities at the nanoscale. And this second goal drives the evaluation in this report.

The nanotechnology community has been growing since the 1980s. State governments now support university nanotechnology-user facilities, television programs and movies envision what a future with nanotechnology could look like, college students select majors in nanotechnology rather than chemistry or materials engineering, and industry considers the tradeoffs in manufacturing nanotechnology and what producing nanomaterials means for workers' health. And since 2001 and the 21st Century Nanotechnology Research and Development Act, the Federal Government began to give a greater share of its research and development dollars to nanotechnology research and development and a greater share of Federal effort to coordinate those investments.

The nanotechnology community is at a turning point. The research efforts of the last decade have delivered impressive understanding of the fundamental science relevant at the scale of individual nanoparticles and nanotubes. Efforts are now delivering equally important results as these "components" are assembled into nano- and meta-scale systems-product concepts. In parallel, the nanotechnology community's engagement with its stakeholders and the public has also matured. The community needs to consider what it wants to accomplish since the resources from universities, institutes, industrial facilities, Federal dollars, philanthropic foundations, and public interest are not infinite and come at an opportunity cost.

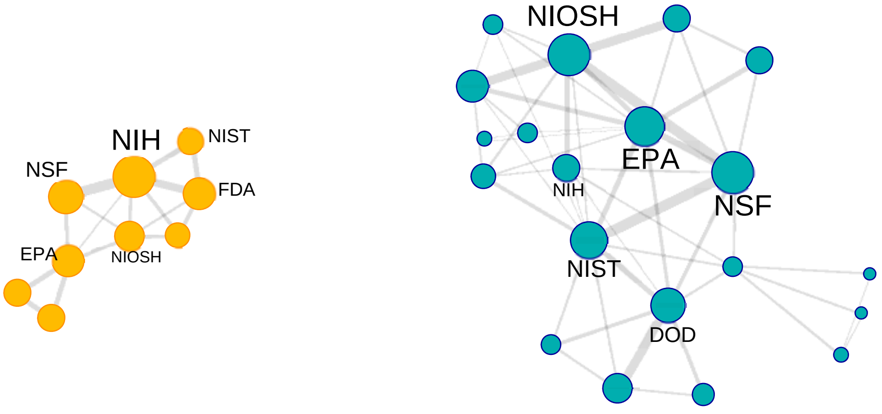
In light of the progress made and cognizant of budget pressures and potentially competing priorities for Federal investment, the NNI needs to have a clear, executable vision for how to maximize the return on the substantial investments that have been made. Continuing to obtain new knowledge, developing new commercial devices, and improving processes or systems that enhance commercial transitions are critical steps to achieve that goal.

The promise of nanotechnology is great. It can potentially transform medicine, security, transportation, agriculture, and more, but for better or for worse, the future will also be shaped by competing technologies and approaches. During this transition, the nanotechnology community needs leaders who will articulate a vision for the community's future and who will develop strategic plans for what the community wants to accomplish.

We review in this report the actions and investments of one segment of this community: the Federal Government.

Federal Government's Role in Nanotechnology

The NNI vision is "a future in which the ability to understand and control matter at the nanoscale leads to a revolution in technology and industry that benefits society." [10] The Government's role so far in unlocking the potential of this technology has been to ensure that the activities within the U.S. Government are well coordinated. Since the NNI was launched in 2001, the Federal Government has brought together an increasing number of nanotechnology activities across its agencies. From FY2005 to FY2014 alone, 628 agency-to-agency collaborations resulted, growing from 35 such collaborations in FY2005 to 159 collaborations by FY2013 (Figure 1). Along with coordinating individual activities, in 2010 the Government's interagency process began to spotlight Nanotechnology Signature Initiatives (NSIs), which are rotating areas of national interest that involve investment and coordination of at least three Federal agencies. The collaborations around some of these NSIs have blossomed.



35 collaborations
FY2005-FY2006

159 collaborations
FY2013-FY2014

Figure 1. Federal interagency collaborations in NNI increased over four-fold in eight years.

After 13 years, the success of the first phase of activities and the maturation of the research field has placed the field of nanotechnology at a critical transition point. Success stories from just the past two years are evident in Boxes 1 and 2. We call the next phase of nanotechnology development NNI 2.0. In reviewing the Federal activities in nanotechnology, we sought to identify how best to invest Federal funds and to coordinate and lead Federal activities in the next decade. Strong management of program activities in commercialization, in the research enterprise, and in environmental, health, and safety issues remain as the core concepts. Whether our vision for NNI 2.0 is adopted or an incremental evolution of today's NNI is selected, the choice to have an initiative implies continuing to choose to make nanotechnology a distinct field of Federal Government focus.

Box 1. Nanotechnology Success Story #1

Light- and Heat-Shielding Nano-Coating for "Smart Glass" Developed at the Lawrence Berkeley National Lab

Researchers at the Lawrence Berkeley National Laboratory (LBNL) have developed an electrochromic composite nanomaterial that can be applied to glass to alter electronically the transmission of light and heat through the glass surface [1]. Electrochromic materials change color reversibly when a charge is applied. Electrochromic material-coated glass is currently marketed as "smart glass" and can transition between transparent and opaque states when a switch is flipped. Smart glass can improve temperature control or lighting systems, provide privacy, or act as a projection screen. LBNL researchers embedded indium tin oxide nanocrystals in an electrochromic glass to develop a nanocrystal-in-glass composite. Properties of the nanocrystals keep certain infrared wavelengths from passing through the coating, and the glass material screens visible light. Using the two materials in a composite allows light and heat transmission to be controlled separately, and it makes the glass five times more electrochemically active so that researchers could use thinner and more transparent coats of the material. The system requires very little energy – a square-meter window coated in the composite material could be powered by a 9-volt battery for a year – making it much less expensive than current systems. It is also entirely solution-based and could be developed into a spray form. Researchers have launched a startup and are working to scale production and develop partnerships with the glass and building technologies industries.

Box 2. Nanotechnology Success Story #2

Nanotube-Infused Clothing May Protect Against Chemical Weapons

A research team at the National Institute of Standards and Technology (NIST) has completed a proof-of-concept demonstration of carbon nanotubes that degrade a class of chemical nerve agents and could be incorporated into fabrics to create protective clothing [2]. This class of nerve agents includes sarin, which was used in a 1995 bioterrorism attack in the Tokyo subway and more recently in the conflict in Syria. When absorbed into the body, these chemicals disrupt processes ranging from muscle contraction to high-level cognition and lead to long-term physiological and psychological damage and even asphyxiation at high exposures. In the NIST experiments, single-wall carbon nanotubes were bonded to a catalyst. Properties of the nanotubes improve the rate of catalysis to 63 times the untreated rate and maintain catalytic ability for several weeks. The nanotubes are flexible and lightweight with high tensile strength, making it likely that a fabric containing this material would be highly wearable in addition to self-decontaminating. This technology has the potential to protect both civilians and warfighters from chemical weapons and to improve the safety of cleanup operations. Researchers are working to increase the speed of the reaction and to determine the best method for incorporating the material in the fabric while maximizing its catalytic ability.

This introduction outlines the current organization of Federal activities under the National Nanotechnology Initiative and describes the state of international competition. In subsequent chapters, we evaluate and make recommendations on areas of program management; commercialization; research; and environmental, health, and safety (EHS) issues to realize the potential of this important field.

Organization of the National Nanotechnology Initiative

Numerous Federal agencies invest in nanoscience and nanotechnology. The President coordinates national science, technology, and space policy through the National Science and Technology Council (NSTC) [11]. NSTC's Committee on Technology has established its **Nanoscale Science, Engineering, and Technology** (NSET) Subcommittee to coordinate Federal activities with the National Nanotechnology Initiative vision. In addition to its formal relationship to the Committee on Technology, NSET also maintains a less formal relationship to NSTC's Committee on Science.

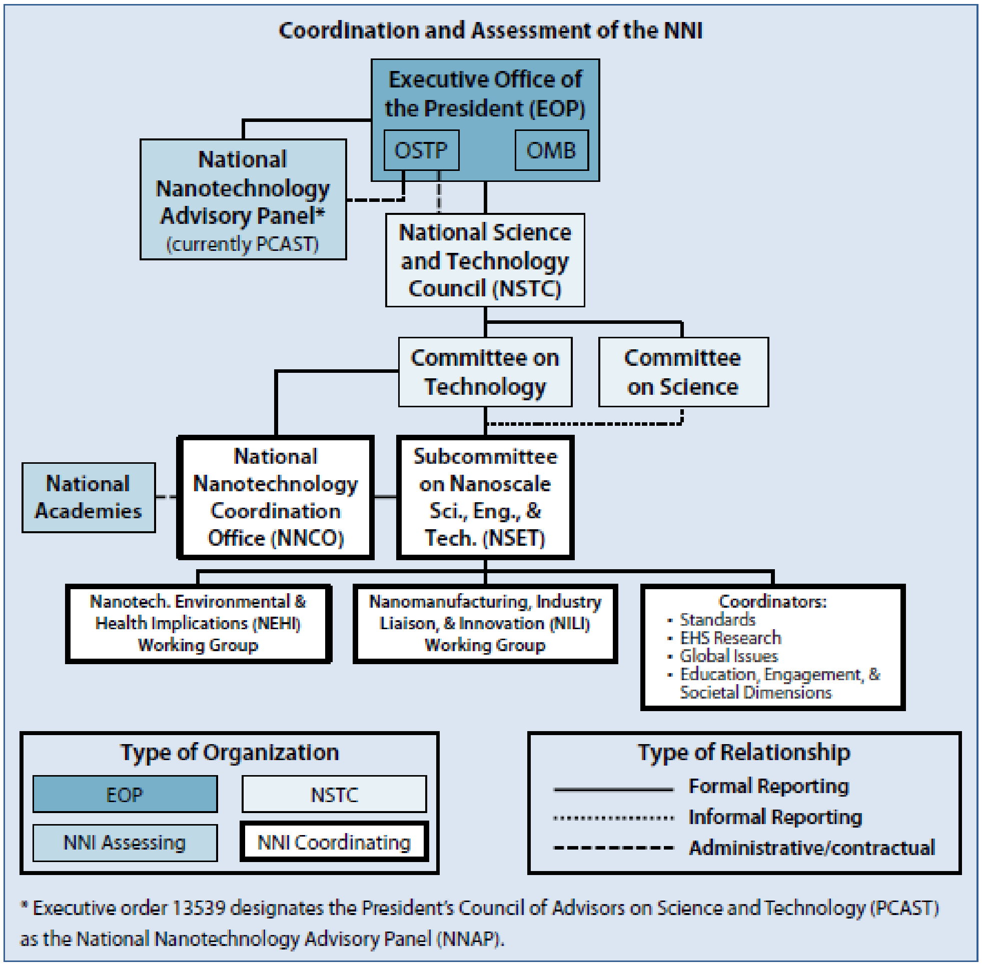
NSET membership consists of representatives from the more than 20 Federal agencies that have interests in nanotechnology, including more than 11 that are funding or have funded nanotechnology efforts over the history of the initiative, as well as representatives from the Office of Science and Technology Policy (OSTP) and the Office of Management and Budget (OMB) [12].

NSET currently charters two **Working Groups** to aid in its coordinating efforts [13]. These are:

> **The Nanotechnology Environmental & Health Implications Working Group (NEHI)** to provide a forum for focused interagency collaborations on EHS and leadership in establishing the national nanotechnology EHS research agenda, in addition to communicating EHS information amongst Federal agencies and to the public. NEHI participants include those agencies that are involved in policy, education, and science aspects of public, workplace, and environmental safety.
>
> **The Nanomanufacturing, Industry Liaison & Innovation Working Group (NILI)** to promote collaboration and partnerships across the broadest possible Federal, State, and private sectors to build U.S. leadership in the products and services that are and will be enabled by nanotechnology.

In addition to its Working Groups, NSET has appointed four **Coordinators** from across its members to strengthen interagency coordination on topics deemed critical to the success of nanotechnology development. Current Coordinators include the Coordinator for Standards Development; the Coordinator for Environmental, Health, and Safety Research; the Coordinator for Global Issues; and the Coordinator for Education, Engagement, and Societal Dimensions.

Central support to NSET as well as to the broader Federal investment in nanotechnology is provided by the **National Nanotechnology Coordination Office** (NNCO). NNCO was authorized in 2003 [3]. It assists in public outreach, serves as a point of information exchange, and promotes access to foundational nanotechnology science and its emerging applications. The Office coordinates much of the public face of the Initiative, including staging meetings and workshops of the NSET and its working groups. NNCO coordinates preparation and publication of NNI interagency planning, budget, and assessment documents, and maintains the NNI website, http://www.nano.gov. NNCO is funded by NSET Subcommittee agency contributions [14]. Figure 2 shows the organization chart for the various participants in the NNI.



* Executive order 13539 designates the President's Council of Advisors on Science and Technology (PCAST) as the National Nanotechnology Advisory Panel (NNAP).

Figure 2. In the Federal structure committed to the vision of NNI, the Subcommittee on Nanoscale Science, Engineering, and Technology coordinates many interagency activities [15].

Funding the National Nanotechnology Initiative

Federal activities in nanotechnology range from investments in foundational research to efforts aimed at enabling commercial applications of nanotechnology-enabled products and solutions. Primary funding streams support individual and team-based research, a variety of multidisciplinary centers, and significant user facilities as part of the infrastructure necessary to support these research efforts. Activities relating to environmental, health, and safety concerns, as well as the development of policy frameworks to understand, educate, and guide the ethical, social, and legal implications of emerging nanotechnology, are also funded by Federal agencies.

Federal budgets for nanotechnology are developed by individual participating agencies and, as such, fit within the overall prioritization and approval process of those organizations, subject to review and approval by the Office of Management and Budget. The NNCO aggregates individual agency budget requests for nanotechnology and Congressional appropriations into a comprehensive annual report to provide visibility to the overall national investment in nanotechnology. The most recent report is the FY2015 NNI Budget Supplement [16].

Spending by agency has been reasonably stable over the last four years, with the notable exception of a 60% drop in Department of Defense (DOD) spending between 2012 and 2013, as sequestration and budget-reconciliation decisions were made. Historical nanotechnology funding by agency is detailed in Table 1, and the FY2015 request for funding by Program Component Areas is in Table 2 [17]. As shown in Table 1, funding peaked for nanotechnology in 2010 at approximately $1.9 billion, dropped slightly to approximately $1.85 billion in both FY2011 and 2012, then dropped nearly 17% to the 2013 level. American Recovery and Reinvestment Act funding injected over $500 million in additional funds into the NNI, primarily at the Department of Energy (DOE), the National Institutes of Health (NIH), National Institute of Standards and Technology (NIST), and the National Science Foundation (NSF). Nanotechnology funding levels for 2014 are $1.537 billion; essentially flat to 2013's $1.550 billion on a non-inflation adjusted basis. As has been typical of recent years, five agencies account for over 93% of nanotechnology investments in the FY2015 budget proposal: NIH (28.7%), NSF (26.8%), DOE (22.3%), DOD (9.4%), and NIST (5.4%).

Overview of the Remainder of this Report

Evaluating the structure of the Federal investments in nanotechnology, the progress on the four goals of the NNI, the state of international collaboration and competition, and engaging in numerous conversations with members of the nanotechnology community brought up many ideas for PCAST to consider about the Federal Government's activities in nanotechnology. The primary conclusion of our review is that the United States will be able to claim the rewards that come from investing in nanotechnology research and an overarching Federal initiative only if the Federal interagency process, the Office of Science and Technology Policy, and the agencies themselves transition their nanotechnology programmatic efforts beyond primarily just supporting and coordinating basic and applied research toward building frameworks for translating the technologies into commercial products. To ensure that NNI 2.0 is a successful and vibrant initiative, we recommend the coordinated use of the Grand-Challenge framework as an overarching program-management structure, as has been effectively practiced in other parts of the U.S. Government research and development system. Grand Challenges are meant to align stakeholders across the nanotechnology community toward delivering transformative technologies. This Grand-Challenge framework in the U.S. Government must be supported by the development of an advisory committee to the NSET and the development of metrics to monitor the progress of Federal nanotechnology investment. We believe that by focusing on Grand Challenges, continuing to support vital discovery and exploratory research, and continuing an active collaborative and competitive international engagement, NNI 2.0 will deliver on the promises now emerging from the highly successful first phase of the National Nanotechnology Initiative. We note specifically that the focus on commercialization in NNI 2.0 should not preclude it from investing in and coordinating discovery and exploratory research, which is the bedrock on which commercial technology builds.

The 2014 NNI review report is organized into chapters around categories of recommendations. The chapters following this introduction are organized as follows:

1. NNI Goals and Progress – the status of the science
2. Grand Challenges for NNI 2.0 – the mechanism behind NNI 2.0
3. Program Management – the organizational structure of the Federal component of NNI 2.0
4. Commercialization – the path to commercialization needed under NNI 2.0
5. Research Enterprise – the discovery and exploration breakthroughs needed under NNI 2.0
6. Environmental, Health, and Safety Issues – the development of an EHS strategy under NNI 2.0

We also include an appendix and offer an example of how to measure the continuum of the research / translation process and subsequent outcomes.

Each of the chapters relate back to the core premise of this report, that a Grand-Challenge framework will provide the necessary mechanism to motivate stronger cross-agency partnering and the building of an ecosystem bringing together government, industry, and academia. In the end, if the lines between nanotechnology and other technologies are blurred in the drive to fulfill these Grand Challenges and nanotechnology becomes part of the greater research and translation portfolio, NNI 2.0 should be viewed as a great success.

Table 1. NNI investments from FY2001 to FY2015 (request). Data provided by NNCO.

National Nanotechnology Initiative Investments by Agency
FY 2001-2015 (dollars in millions)

FY	2001	2002	2003	2004	2005	2006	2007	2008	2009†	2010	2011	2012	2013	2014††	2015†††	Total*
CPSC	0	0	0	0	0	0	0	0	0.2	0.5	1.8	2.0	1.3	2.0	2.0	**9.7**
DHS	0	2	1	1	1	1.5	2.0	3.2	9.1	21.9	9.0	18.7	14.0	24.0	32.4	**140.7**
DOC / NIST	33	77	64	77	79	77.9	87.6	85.6	93.4	114.7	95.9	95.4	91.4	97.8	82.6	**1252.3**
DOD	125	224	220	291	352	423.9	450.2	460.4	459.0	439.6	425.3	426.1	170.1	175.9	144	**4786.4**
DOE	88	89	134	202	208	231	236	244.7	332.6	373.8	346.2	313.8	314.2	303.3	343.1	**3759.7**
DOJ	1	1	1	2	2	0.3	1.7	0.1	1.2	0.2	0.0	0.0	0.0	0.0	0.0	**10.5**
DOT	0	0	0	0	0	0.9	0.9	0.9	0.9	3.2	1.0	1.0	2.4	2.0	1.5	**14.7**
EPA	5	6	5	5	7	4.5	7.6	12.1	11.6	17.7	17.4	17.5	14.6	15.5	16.8	**163.3**
DHHS (total)	40	59	78	106	168	195.4	222.7	311.4	356.0	472.6	428.543	479.6	485.4	469.5	469.6	**4341.7**
FDA	0	0	0	0	0	0	0	0	6.5	7.3	9.9	13.6	16.1	17.0	17.0	87.4
NIH	40	59	78	106	165	191.6	215.4	304.5	342.8	456.8	408.6	456.0	458.8	441.5	441.5	4165.4
NIOSH	0	0	0	0	3	3.8	7.3	6.9	6.7	8.5	10.0	10.0	10.5	11.0	11.1	88.8
NASA	22	35	36	47	45	50	19.8	17.4	13.7	19.7	17.0	18.6	16.4	17.9	13.7	**389.2**
NSF	150	204	221	256	335	359.7	388.8	408.6	408.6	428.7	485.1	466.3	421.0	410.6	412.4	**5355.8**
USDA (total)	0	0	0	2	3	6.2	6.8	10.1	15.3	20.313	20	18.317	19.498	19.07	18.8	**159.4**
ARS	0	0	0	0	0	0	0	0	0	0	0	2.0	2.0	2.0	2.0	8.0
FS	0	0	0	0	0	2.3	2.9	4.6	5.4	7.1	10.0	5.0	5.0	4.0	4.0	50.3
NIFA	0	0	0	2	3	3.9	3.9	5.5	9.9	13.2	10.0	11.3	12.5	13.1	12.8	101.1
TOTAL†	**464**	**697**	**760**	**989**	**1200**	**1351.3**	**1424.1**	**1554.5**	**1701.5**	**1912.8**	**1847.3**	**1857.3**	**1550.2**	**1537.5**	**1536.9**	**20383.4**

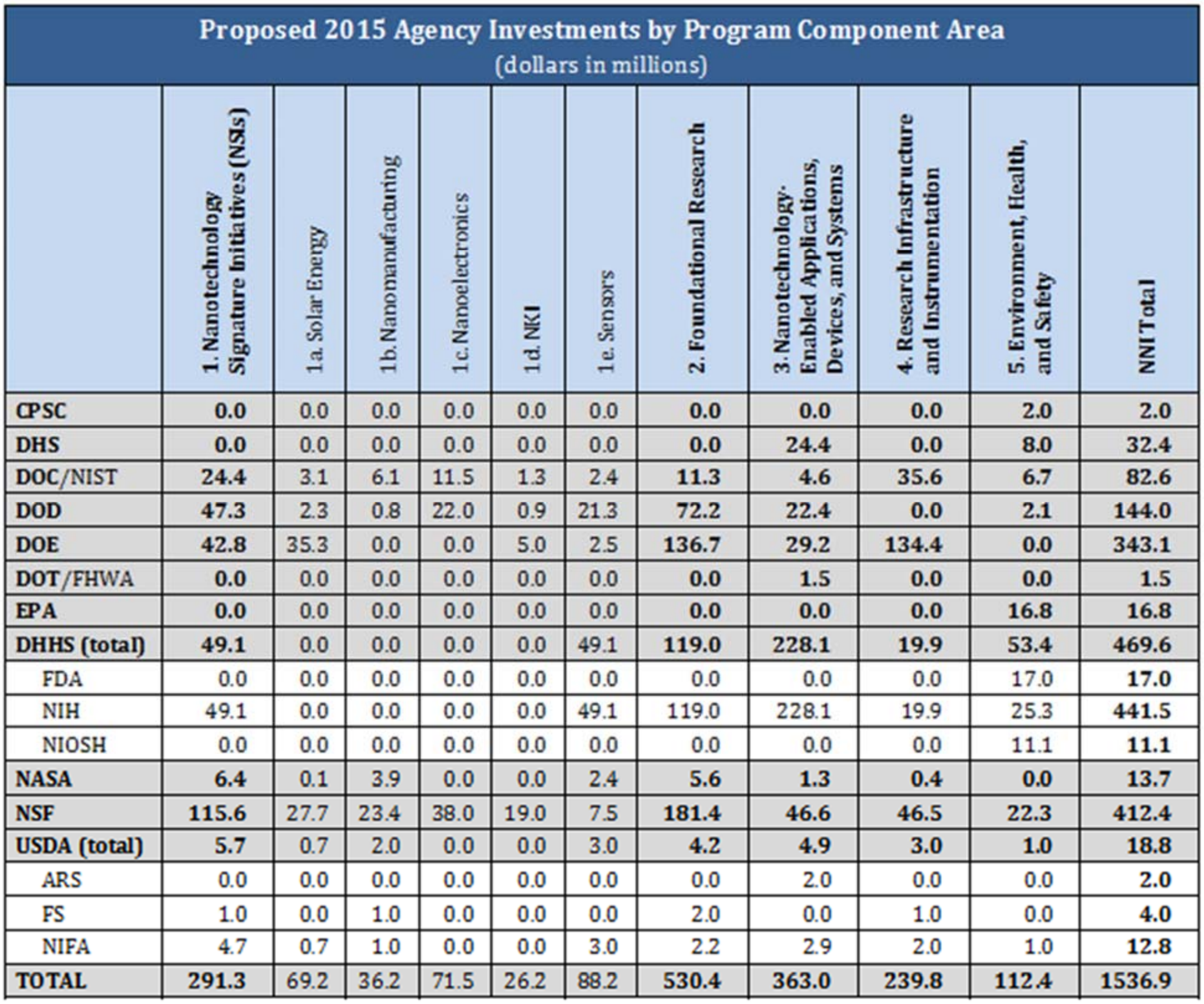
* NOTE: Totals may not add due to rounding

† NOT including American Recovery and Reinvestment Act funds for NSF ($101 M), DOE ($293 M), NIST ($43 M), and NIH ($73 M)

†† FY '14 estimated based on 2014 enacted levels and may shift as operating plans are finalized

††† FY '15 Request

Table 2. FY2015 request for funding by Program Component Area from the National Nanotechnology Initiative Supplement to the President's 2015 Budget.



Proposed 2015 Agency Investments by Program Component Area
(dollars in millions)

	1. Nanotechnology Signature Initiatives (NSIs)	1a. Solar Energy	1b. Nanomanufacturing	1c. Nanoelectronics	1d. NKI	1e. Sensors	2. Foundational Research	3. Nanotechnology-Enabled Applications, Devices, and Systems	4. Research Infrastructure and Instrumentation	5. Environment, Health, and Safety	NNI Total
CPSC	**0.0**	0.0	0.0	0.0	0.0	0.0	**0.0**	**0.0**	**0.0**	**2.0**	**2.0**
DHS	**0.0**	0.0	0.0	0.0	0.0	0.0	**0.0**	**24.4**	**0.0**	**8.0**	**32.4**
DOC/NIST	**24.4**	3.1	6.1	11.5	1.3	2.4	**11.3**	**4.6**	**35.6**	**6.7**	**82.6**
DOD	**47.3**	2.3	0.8	22.0	0.9	21.3	**72.2**	**22.4**	**0.0**	**2.1**	**144.0**
DOE	**42.8**	35.3	0.0	0.0	5.0	2.5	**136.7**	**29.2**	**134.4**	**0.0**	**343.1**
DOT/FHWA	**0.0**	0.0	0.0	0.0	0.0	0.0	**0.0**	**1.5**	**0.0**	**0.0**	**1.5**
EPA	**0.0**	0.0	0.0	0.0	0.0	0.0	**0.0**	**0.0**	**0.0**	**16.8**	**16.8**
DHHS (total)	**49.1**	0.0	0.0	0.0	0.0	49.1	**119.0**	**228.1**	**19.9**	**53.4**	**469.6**
FDA	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	17.0	**17.0**
NIH	49.1	0.0	0.0	0.0	0.0	49.1	119.0	228.1	19.9	25.3	**441.5**
NIOSH	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	11.1	**11.1**
NASA	**6.4**	0.1	3.9	0.0	0.0	2.4	**5.6**	**1.3**	**0.4**	**0.0**	**13.7**
NSF	**115.6**	27.7	23.4	38.0	19.0	7.5	**181.4**	**46.6**	**46.5**	**22.3**	**412.4**
USDA (total)	**5.7**	0.7	2.0	0.0	0.0	3.0	**4.2**	**4.9**	**3.0**	**1.0**	**18.8**
ARS	0.0	0.0	0.0	0.0	0.0	0.0	0.0	2.0	0.0	0.0	**2.0**
FS	1.0	0.0	1.0	0.0	0.0	0.0	2.0	0.0	1.0	0.0	**4.0**
NIFA	4.7	0.7	1.0	0.0	0.0	3.0	2.2	2.9	2.0	1.0	**12.8**
TOTAL	**291.3**	69.2	36.2	71.5	26.2	88.2	**530.4**	**363.0**	**239.8**	**112.4**	**1536.9**

Chapter 2. NNI Goals and Progress

From the outset, the NNI was envisioned with broad and far-reaching ambitions, with the ultimate outcome of societal benefits [10]. Four goals were defined:

(1) To advance world-class nanotechnology research and development;

(2) To foster the transfer of new technologies into products for commercial and public benefit;

(3) To develop and sustain educational resources, a skilled workforce, and the supporting infrastructure and tools to advance nanotechnology; and

(4) To support the responsible development of nanotechnology.

Over twelve years have passed since these NNI ambitions were established, and it is fair to assess how well the United States has progressed towards these aims. While perfect metrics to report progress towards these goals do not exist, this review reiterates the need to develop measurements that can be applied to specific Federal program elements while drawing on available measurements to judge overall NNI progress [18]. A brief assessment is performed here with the goal of calibrating the magnitude of achievement.

With respect to Goal 1 (to advance world-class nanotechnology research and development), Figure 3 reports on nanotechnology research and development through the number of papers and patents published by authors in the United States and other leading nanotechnology regions [19]. The dramatic increase in published papers demonstrates the United States' commitment to nanoscience research over the life of the NNI. While the rate of patents published in three or more countries has decreased over the past decade, the cumulative growth of nanoscience patents follows an S-curve technology-development model suggesting that the field of nanotechnology product development is growing toward, but has not yet reached, maturity [20]. Together, these data demonstrate the clear creation of nanoscience knowledge and the United States' position as a global leader in the field.

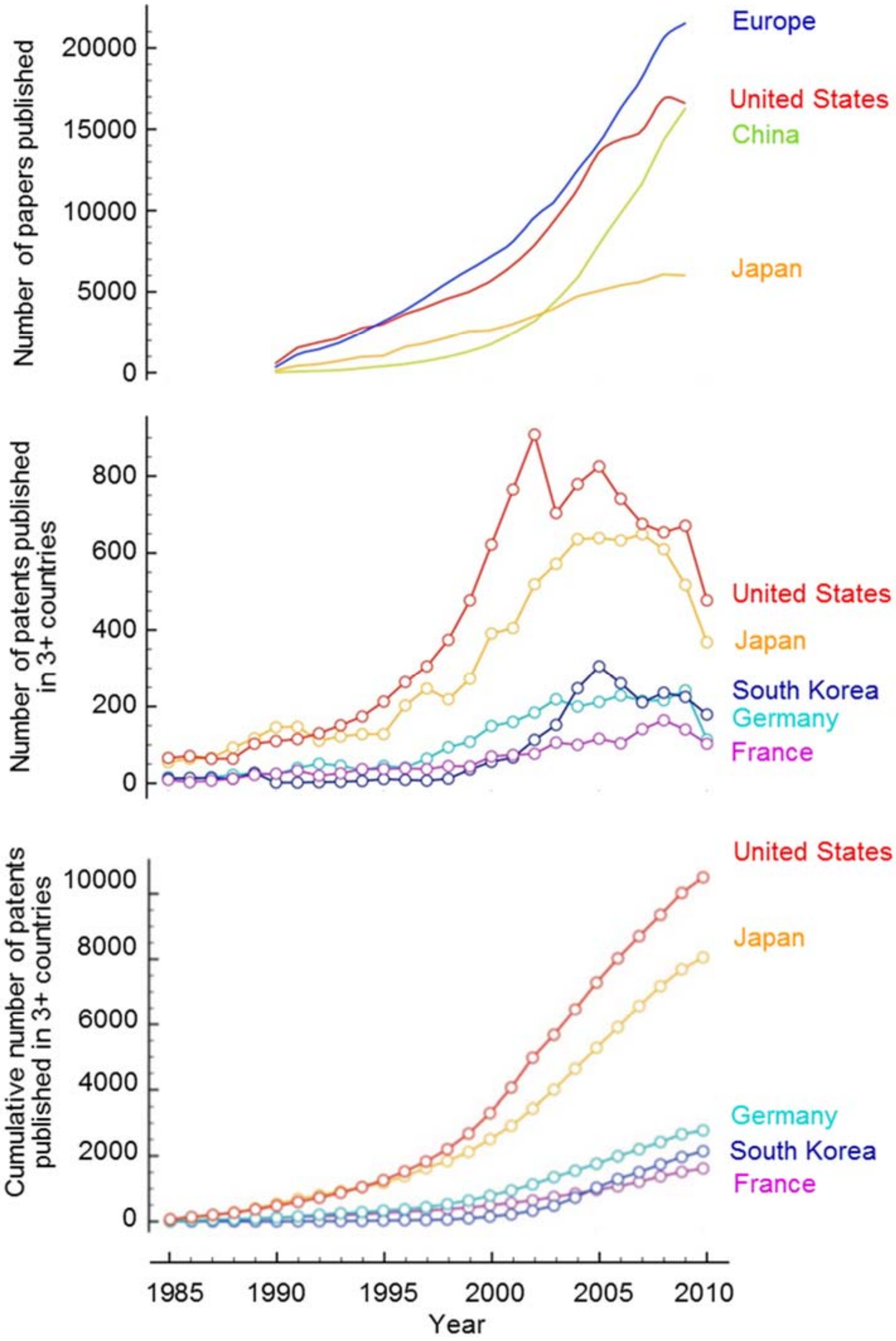


Figure 3. NNI Goal 1. Number of published papers and patents for the United States and other international leaders. The metric of patents published in three or more countries is a more representative indicator of significance compared with patents published in just one or two countries [19] [21].

With respect to Goal 2 (to foster the transfer of new technologies into products for commercial and public benefit), Figure 4 reports on the commercialization of nanotechnologies using the measured (2003-2009) and predicted (2010-2015) nano-enabled products revenue in the United States and other global regions [22]. Although some market revenue has been demonstrated, these data suggest that the full market potential of nanoscience has yet to be achieved. The magnitude of the revenue predicted – up to $20 billion in the United States in 2015—is considerable, demonstrating that nanotechnology has the potential to contribute significantly to our economy. Again, the United States is a leader in the field, with Europe and the Asia-Pacific region as close competitors.

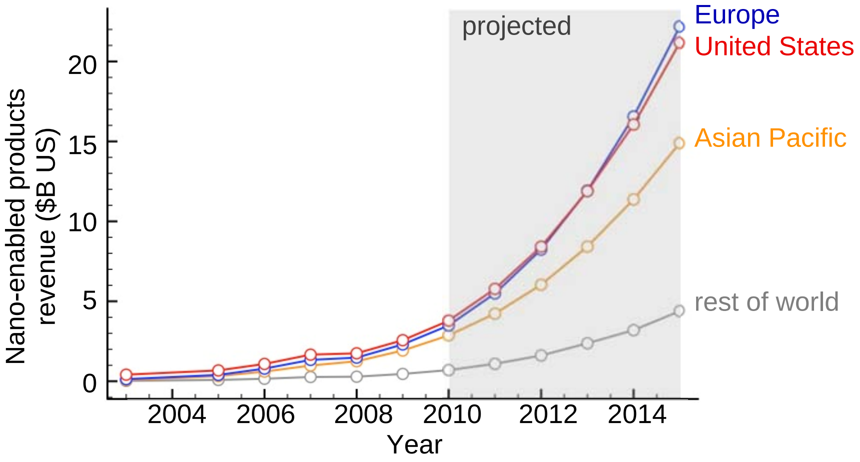


Figure 4. NNI Goal 2. Nano-enabled products in the United States and other regions are increasing their market revenue, with significantly increasing growth rates predicted for the coming years. Data from Lux Research.

With respect to Goal 3 (to develop and sustain educational resources, a skilled workforce, and the supporting infrastructure and tools to advance nanotechnology), Figure 5 reports on the development of the nanotechnology workforce and infrastructure. The number of existing Federally funded nanoscience centers, typically large-scale endeavors where faculty and students from many departments and even different institutions share ideas and collaborate, can be used to indicate educational and workforce development activities. The number of centers increases over the years and starts to plateau in 2010. The reported data take into account both the creation of new centers, as well as the sunsetting of centers for which funding has expired [23]. The number of users at Federally funded nanoscience-research facilities, which often house advanced equipment for nanoscale research – for example, transmission and scanning electron microscopes, various spectroscopic instruments, and electron and ion beams for lithography – can be used to indicate the creation of infrastructure and tools, as well as education, training, and workforce development. The Department of Energy Nanoscale Science Research Centers (DOE NSRCs) have increasingly provided equipment, training, and access to users. DOE reports up to roughly 400 users per center in 2012, an average of one user per day for a given center.

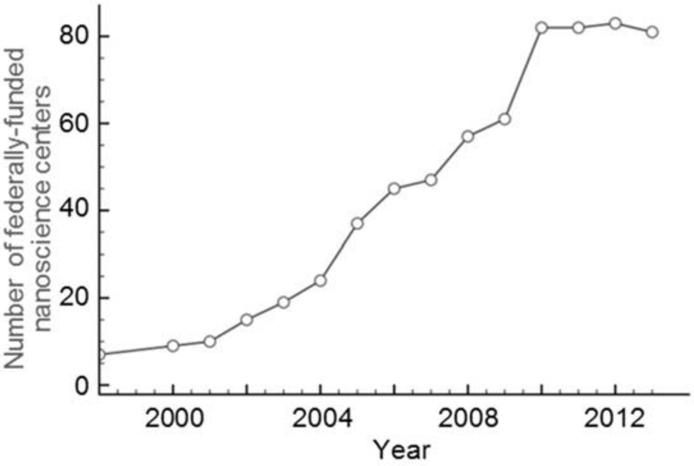


Figure 5. NNI Goal 3. Infrastructure and workforce training has developed in the United States over 12 years, with the growth of Federally funded nanoscience centers and user facilities. Data gathered from NNI and Federal agency websites.

Figure 6 attempts to assess Goal 4 regarding the responsible development of nanotechnology. Federal investments in nanoscience research related to Environmental, Health, and Safety (EHS) and Educational, Ethical, Legal, and Societal Issues (EdELSI) are plotted in both absolute dollars and as a percent of total NNI funding. These Federal investments certainly demonstrate "support." The responsible development of nanotechnology has not been fully achieved – consider, for example, the lack of clear regulations and the many unknowns regarding EHS effects emerging at the nanoscale. While some progress has been made towards the five research categories identified in 2008 as NNI EHS priority strategies, the sheer range of chemical compositions, sizes, and shapes encompassed in the category "nanomaterials" ensures a considerable task in accurately characterizing each material and ultimately developing effective EHS policies [24]. Much work remains to be done in this area.

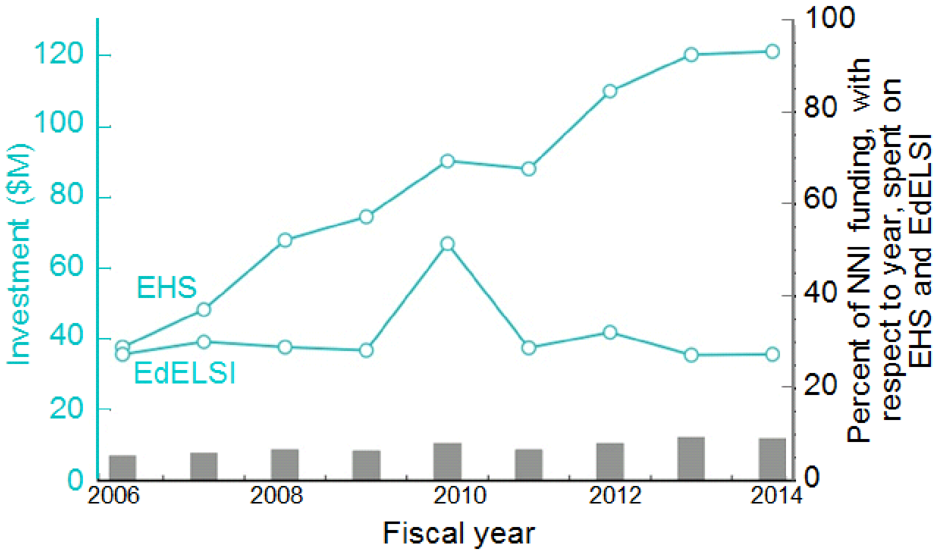


Figure 6. NNI Goal 4. U.S. EHS and EdELSI investments in dollars (left ordinate and traces) and as a percentage of total NNI funding (right ordinate and bars). FY2009 and FY2010 data include ARRA funding; FY2013 and FY2014 data report estimated and requested amounts, respectively. Data gathered from http://nanodashboard.nano.gov.

The data presented here provide one view of NNI accomplishments, and they demonstrate that clear progress has been made. But much work remains in order to accomplish the goals of the NNI, which was conceived as a long-term endeavor [25]. The development of metrics that more fully capture NNI achievements, coupled with the collection of data for these metrics, will provide an increasingly accurate assessment of the NNI.

International Collaboration and Competition

The Federal Government's nanotechnology research, commercialization, regulation, and ultimately societal benefit unfold in a global context. A 2014 evaluation of nanotechnology publications for 2011-2013 shows that China and the European Union have led the United States in numbers of nanotechnology publications, with China publishing the most papers in nanotechnology for the first time in 2013 (Figure 7). Increases in spending overseas have made nanotechnology commercialization and particularly nanotechnology manufacturing a national priority in many countries. Over 60 countries have invested in nanotechnology at the national level [19]. As of 2012, the top four individual countries with national nanotechnology investments were the United States (Federal and states $2.1 billion), Japan ($1.3 billion), Russia ($974 million), and Germany ($617 million). Creating and maintaining a separate, coordinated nanotechnology effort at a national scale, as in the United States and Germany, is an approach some countries, such as Japan and Russia, have moved away from as initiatives expire and nanotechnology applications become integral to multiple facets of broader science and technology funding. In 2011, Japan cut nanotechnology as a focus area and integrated it with the larger funding plan while continuing to increase federal nanotechnology support from $918 million in 2010 to $1.3 billion in 2012.

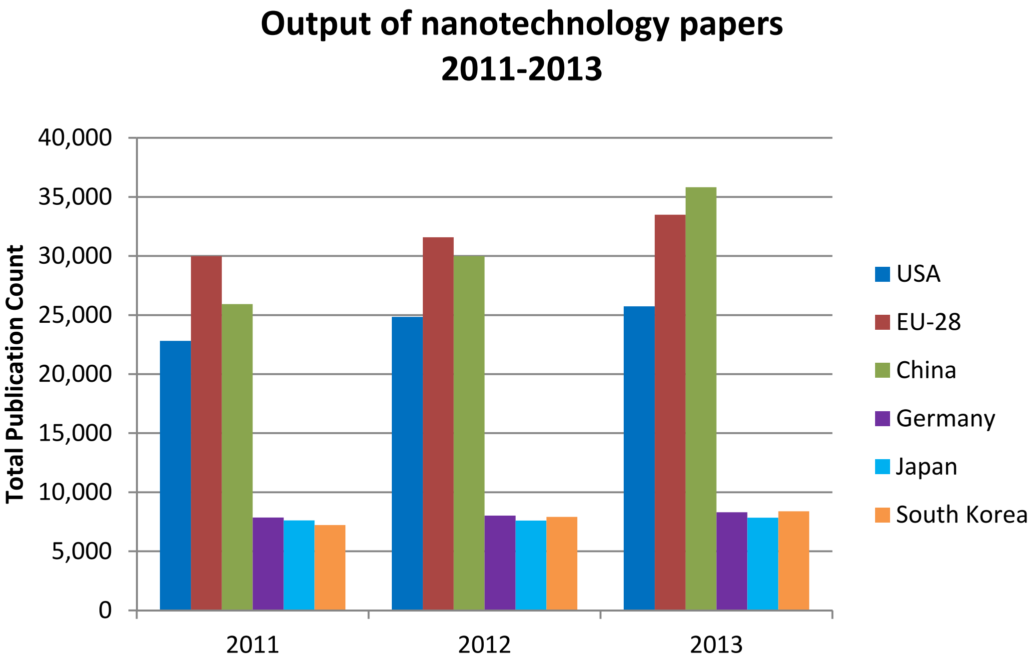


Figure 7. From 2011 to 2013, the United States, European Union, and China produced the largest numbers of nanotechnology papers published each year, with China leading [26] [27].

Another important direction of NNI 2.0 leadership will be to help determine where the United States best competes with other countries and where it should collaborate. The NNI Strategic Plan released by the Office of Science and Technology Policy (OSTP) in February 2014 remarks that the United States should be actively engaged “in international activities integral to the development and responsible commercialization of nanotechnology-enabled products and processes.” [28] This includes (i) participating and leading the development of international nanotechnology standards; (ii) engaging in bilateral and multilateral collaborations and cooperative activities to further nanotechnology-related commercialization, innovation, and trade; and (iii) supporting forums in which U.S. and international stakeholders can exchange technical information and discuss market needs, intellectual property rights, and other issues relevant to enabling commercialization.

The call for collaboration supports the development of revolutionary new technology that has far-reaching implications for innovation, economic development, and the advance of sustainable scientific enterprises. Accordingly, OSTP has bilateral science agreements with Russia, China, India, Brazil, Japan, and South Korea. The Unites States’ international participation in nanotechnology activities benefits all sides in knowledge exchange, increased trade, and economic growth, and it also catalyzes U.S. leadership in a growing global nanotechnology enterprise that is expected to attain a global value of $4.4 trillion by 2018 [22].

The DOE Nanoscale Science and Engineering Centers, for example, accept proposals to conduct fundamental research in the Centers regardless of the proposal's country of origin. The winning proposals are those with the highest scientific merit, bringing the highest quality research to the United States.

The United States also benefits from international collaboration by attracting the brightest and best-educated graduates from outside the country to work in U.S. universities and industry. In the United States, they infuse their advanced knowledge, skills, and fresh ideas into the U.S nanotechnology enterprise. Because of the breadth and depth of the U.S. research enterprise and translation of intellectual property into new commercial opportunities, international collaboration has contributed to expansion of the global nanotechnology enterprise and trade opportunities that has benefited the U.S. economy.

While the development of electronics, energy generation, batteries, supramolecular chemistry, synthesis through self-assembly, biotechnology, and nanomedicine are transparent worldwide academic and industrial enterprises, the advent of molecular nanofabrication could drastically change the balance of leadership in nanotechnology. It will require extraordinarily complicated and revolutionary advances in knowledge, but the ability to produce nano-inspired molecular manufacturing could spawn a technical revolution. As with all dual-use technologies, the impact of malicious use must be considered.

How should the United States deal with these contrasting scenarios in evaluating its international collaborations and agreements? Staying competitive and actively engaged in the international nanotechnology enterprise would appear to be the best option, not only from a global economy perspective, but also having access to the ever-growing nanoscience and nanotechnology knowledge base and toolbox. This will allow the United States to develop its own competitive nanomanufacturing enterprise and accompanying awareness of the development of asymmetrical capabilities that may require further scrutiny.

Next Generation Nanotechnology Research

Balancing the focus on Grand Challenges and with the awareness of collaborative and competitive international engagement, NNI 2.0 will need to continue to invest in and coordinate discovery and exploratory research in nanotechnology. Research and development in nanotechnology during this second phase of investment will seek to bring reproducible atomic-scale control to nanoscale building blocks, build active nanostructures instead of passive ones, and integrate nanoscale elements into complex assemblies with emergent and, ultimately, predictable properties. Nanotechnologies with these properties could transform energy, advanced materials, electronics, medicine, and more. The technical challenges in achieving control, function, and integration of nanoscale building blocks, however, will likely be more difficult than the creation of the nanoscale units themselves. Drawing an analogy to electronics, the discovery of the transistor was only the first step in a long journey to laptops, smartphones, and the internet. The development of a stable workforce and infrastructure is a responsibility that NNI 2.0 should prioritize to be fulfilled by the agencies and the private sector. Many of competitors to the United States have established long-term strategic goals that range up to 2025.

Chapter 3. Grand Challenges for NNI 2.0

Additional leadership and management tools are needed to bring about the transition to NNI 2.0 advocated by PCAST. We recommend that the construct of Grand Challenges be instantiated across the NNI ecosystem and in the management of Federal activities to focus NNI participants on significant problems of major national interest that, by commercializing the associated science and technology, will benefit society. Organizing activities around Grand Challenges can be a major community rallying point and provide additional tools to manage and measure the effectiveness of NNI 2.0.

This chapter provides the details behind this proposed Grand Challenges-based model. To ground the discussion, we first look at one current programmatic element of NSET's activities, the Nanotechnology Signature Initiatives (NSIs). We review progress and effectiveness of the implementation of NSIs and then describe in detail the rationale for and characteristics of Grand Challenges, how they differ from the NSIs, and illustrative examples that could be applicable for NNI 2.0 Grand Challenges. Specific recommendations are then made to instantiate the Grand Challenges construct, with particular focus paid to how to engage the NNI community in identifying and selecting Grand Challenges.

Nanotechnology Signature Initiatives

Beginning with its 2010 strategic planning process, the NSET created focal areas for cross-agency collaboration and coordination, culminating in the creation of five Nanotechnology Signature Initiatives [29]. The NSIs define the shared vision of OSTP and participating Federal agencies for advancing nanoscale science and technology from research to commercialization through enhanced interagency coordination and focused investment. NSIs are selected as broad areas that exhibit particular promise and significant opportunity and that involve three or more Federal agencies. Five topics have been chosen as detailed in the 2014 NNI Strategic Plan [28]. Each is described in a white paper that includes four elements: national need, "thrust areas" or goals, expected outcomes, and agency roles and contributions [30]. The five current NSIs are:

- Nanotechnology for Solar Energy Collection and Conversion: Contributing to Energy Solutions for the Future,
- Sustainable Nanomanufacturing: Creating the Industries of the Future,
- Nanoelectronics for 2020 and Beyond,
- Nanotechnology Knowledge Infrastructure: Enabling National Leadership in Sustainable Design, and
- Nanotechnology for Sensors and Sensors for Nanotechnology: Improving and Protecting Health, Safety, and the Environment.

Within its mandate to review the NNI triennially, the National Research Council Committee in 2013 assessed the framework, planning, and management of the NSIs. The Committee specifically examined the practices, agency collaborations, and progress of the 2011 NSIs and analyzed all five NSI white papers for the inclusion of six characteristics of an effective strategy identified by the Government Accountability Organization (GAO). Table 3 shows the historical, current and requested funding for the NSIs. They determined that only the first two GAO characteristics – purpose, scope, and methods; and problem definition and risk assessment – are addressed adequately by the white papers [31].

Table 3. Total funding for Nanotechnology Signature Initiatives 2011-2015 (dollars, rounded to the nearest million) [16] [28].

	2011 ACTUAL	2012 ACTUAL	2013 ACTUAL	2014 EST.	2015 PROPOSED
Nanomanufacturing	61	56	35	38	36
Solar Energy	88	88	74	67	69
Nanoelectronics	97	92	87	77	72
Nano Knowledge Infrastructure	-	2	8	32	26
Sensors	-	55	77	84	88

The Committee observed that the NSIs are "obvious vehicles for collaboration with the private sector" and highlighted the industry-led Nanoelectronics Research Initiative as a model partnership. They also recommended that each NSI team implement formal interagency plans and expand the white papers to include a strategic plan incorporating the elements described by the Committee. Further, the Committee put forward the success of the NSIs as a measure of success for the NNI and suggested that the NSIs would benefit from roadmapping activities, efforts to tie other NNI activity to NSI goals, and improved communication with researchers whose projects contribute to the NSIs.

Characteristics of a Grand Challenge

While an NSI is shaped by the coordination of three or more Federal agencies around a topic, a Grand Challenge is a large, outward-facing effort with a specific, measurable goal. A Grand Challenge has a well-defined technical goal with a story-telling case that inspires different sectors to invest in achieving the goal. Most Grand Challenges address an issue of significant societal impact. An example is the goal of the DOE SunShot Initiative: "reduce the total costs of photovoltaic solar energy systems by about 75% so that they are cost competitive at large scale with other forms of energy without subsidies before the end of the decade."[32] A nanotechnology Grand Challenge should be audacious but achievable and stimulate the network of activities that will drive scientific ideas to commercial nanotechnology and catalyze new discovery for technologies of the future.

Grand Challenges exhibit other important characteristics:

- They have a measurable end-point. It is clear when they have been reached. As such, they also have a finite, albeit relatively long (probably a decade), lifetime.
- They require advances in fundamental scientific knowledge, tools, and infrastructure for successful completion. In short, when a Grand Challenge is begun, all the resources needed to complete it are not known. As such, it is necessary to recognize and articulate the risks of the undertaking and to mitigate those risks to the maximum extent possible.
- There must be clear milestones en route to the final Grand Challenge goal that are both measurable and valuable in their own right. It is only through monitoring these deliverables that it is possible to tell whether or not the effort is on track to achieve its ultimate objective.
- They are integrating. Their solutions require bringing together multiple disciplines – in many cases, disciplines that do not typically interact. In addition, Grand Challenges span from fundamental science to engineering demonstration and, upon completion, to commercialization.
- They are too big to be undertaken by a single, or even a few, institutions. In fact, one way of mitigating the risk inherent in taking on an effort of this magnitude may be to pursue more than a single approach to the problem, thus involving even more institutions than would be engaged in a single approach.

Recommendation 1. Establishing Grand Challenges is an effective means for focusing and amplifying the impact of Federal nanotechnology activities. NSET and OSTP should identify a list of candidate nanotechnology Grand Challenges that address significant societal needs. At least one Grand Challenge should contain program elements aimed at manufacturing challenges specific to that focus area.

Identifying and Implementing Grand Challenges

NSET, the NSTC Committee on Technology, and OSTP have key roles in creating and implementing the process to identify Grand Challenges. This process needs to provide context for the conversations and deliberations that lead up to Grand Challenge selection. Since Grand Challenges will have different lifetimes, depending on their scale and complexity, as well as the resources available to each, Grand Challenge selection and review will be a process that occurs periodically, probably annually.

Recommendation 2. NSET and OSTP should create and execute a process to engage research, development, and industrial stakeholders in the identification and selection of Grand Challenges on an ongoing basis.

Essential elements to identify and implement Grand Challenges include:

- The investment of the public and industrial, academic, national laboratory, investor, financial, and communication sectors.
- A strong leader who is a member of NSET and who can set a vision for a Challenge and convene stakeholders toward its development.
- Identification of critical challenges in the mission space of agencies participating in NNI that have a solution requiring significant advances in nanoscience and technology.
- Understanding of the global landscape in the problem area. What countries are working in the area? How far along are they? What are the prospects of their solving the problem first? If they are ahead, is it likely that we could partner with them, should that be desirable? If they are ahead, is it of critical national importance that we catch up with and/or surpass them?
- Engage broad swaths of stakeholders in the dialogue leading up to Grand Challenge selection. This includes researchers, research managers/leaders, and agency representatives.
- After allowing for significant community engagement, a fairly small set of subject-matter experts and senior advisors should select the Grand Challenges.

We strongly support the participation of the agencies in developing Grand Challenges, including a regular, structured process for creating and supporting new Grand Challenges on an annual basis and reviewing the progress on existing Challenges. One component should be brainstorming workshops where industry representatives, top junior and senior nanoscientists and nanotechnologists, venture-capital firms, and Federal agencies get together with other relevant groups to (a) define a Grand Challenge, (b) identify the roadblocks to progress, and (c) propose ways to address these challenges.

The Federal Government has several possible strategies that could help the nanotechnology community reach the Challenges. The Nanotechnology Faculty Fellows program discussed in Chapter 6 on Research Enterprise could provide a natural leadership base for the conduct of such meetings and evaluation of the ideas developed. Federal agencies can offer innovation prizes that reward the first person or group that achieves one milestone of a Grand Challenge, and they can offer matching funds to competitive applications for public-private partnerships.

Recommendation 3. Federal agencies, with support from OSTP, should offer implementation tools like innovation prizes and public-private partnerships to encourage researchers to reach critical milestones on the path to completing Grand Challenges.

Illustrative Grand Challenges

Thanks to the foundation laid by the NNI, the United States is in a position to move to a new level of integration in nanoscale science and technology in which societal challenges requiring nanoscale science and technology solutions can be addressed by bringing to bear a disciplined, coordinated effort spanning from fundamental scientific discovery to engineering demonstration and commercialization. While the specific challenges to be addressed in the next generation of NNI should be articulated by a process to be developed and implemented by agencies, NSET, and OSTP, a few examples of possible Grand Challenges may help to illustrate the points of this chapter. ***The example Grand Challenges in Boxes 3-6 are only illustrative: actual Grand Challenges will need to be much more clearly articulated and focused, will need to be determined only after extensive community engagement, and will need have their scope and resources carefully aligned***.

Box 3. Illustrative Nanotechnology Grand Challenge #1

Nano-enabled Desalination of Seawater to Solve the Emerging Water Crisis.
The Organisation for Economic Co-operation and Development and the United Nations have reported that 350 million people in 25 different countries are currently suffering from water shortage, and this will grow to 4 billion people (two-thirds of the world population) in 52 countries by 2025. The lack of clean water exacerbates health and energy challenges, making the need to produce clean water one of the most pressing challenges of the 21st century. In most of the world, desalination of sea water is the only possible solution, but the process of desalination remains too energy-intensive to be practical.

Different approaches have been followed in trying to use nanotechnology for desalination, including the incorporation of nanoparticles into existing conventional thin-film composite reverse osmosis (RO) membranes. An alternative approach is to use nanotechnology to create novel nanostructures such as graphene and carbon nanotubes, which could be used as a replacement RO membrane with a highly organized ultrathin structure. These new membranes offer very high selectivity in separating out the salt as the pore morphology can be precisely controlled and energy use can be minimized.

The grand challenge is the reduction in the specific energy consumption of seawater desalination to below 1.5 kWh/m^3.

Box 4. Illustrative Nanotechnology Grand Challenge #2

Reducing Greenhouse Emissions with Nano-enabled Solid-State Refrigeration. Primary power generation to produce the energy required to run heating, ventilating, and air conditioning (HVAC) systems in the commercial and residential built environment is responsible for a significant portion of U.S. greenhouse gas emissions.

Solid-state refrigeration holds the promise of curtailing greenhouse gases, reducing system level noise, and optimizing unit size, weight, and power by more efficiently cooling commercial systems. Thermoelectrics, thermoelastics, electrocalorics, thermionic, and magnetocalorics are the solid-state materials that underlie these systems. The engineering challenge is to improve the materials' performance by reducing the energy lost when energy is converted for cooling in the material (caloric cooling) and by decreasing energy lost at the interfaces between the material and its device and between a single device and the whole system (parasitic loss). Those losses are defined in a Coefficient of Performance (COP). Tailoring materials at the nanoscale could be the basis of significantly superior structures that have higher caloric conversion and reduced parasitic losses.

The Grand Challenge is to develop solid-state cooling systems with COP > 5 (25% higher than current HVAC technologies) and power density > 20 kW/ m^3 (two times greater than current HVAC technology). This will lead to commercial systems that have the potential to reduce greenhouse gas emissions from climate control in buildings by as much as a 20%, resulting in an annual reduction of nearly 200 million metric tons of carbon equivalent emissions, equivalent to removing approximately 40 million passenger cars from U.S. highways.

Box 5. Illustrative Nanotechnology Grand Challenge #3

Creating a New Forefront of Manufacturing through Nano 3D Printing. Three-dimensional (3D) printing is at the forefront of the manufacturing revolution and has the potential to transform U.S. manufacturing and prototyping capabilities in fields as diverse as personalized medical care and vehicle design. The resolution, throughput, and materials flexibility of 3D printing, however, is limited at present. Over the next 10 years, the scientific community should develop 3D-printing technology with the materials flexibility of chemical synthesis and the resolution and throughput of high-cost semiconductor nanofabrication tools in order to create on-demand goods with unique and desirable functions.

Fabrication technologies such as injection molding have the ability to mass-manufacture goods with resolution in the range of hundreds of microns down to hundreds of nanometers; this technique is often cost prohibitive, however, for rapid prototyping and individualized goods. 3D printing has shown great potential in overcoming these limitations, and within the next decade, 3D printing could manufacture large-scale prototypes with precise control over chemical composition, with resolution matching that of modern fabrication techniques, and at a speed and cost that would facilitate wide-spread adoption and household use. With these design aspects perfected, 3D printing will be able to surpass traditional fabrication techniques in the fidelity of manufacturing to design and speed up the manufacturing process. Potential benchmarks toward this goal may be the production of personalized medical devices (e.g., heart stents, replacement joints) at competitive prices to current techniques.

Box 6. Illustrative Nanotechnology Grand Challenge #4

Development of a Nanoscale Therapeutic for at Least One Major Cancer Type by 2030. In spite of impressive advances in our understanding of fundamental cancer biology and the development of a new generation of targeted cancer therapies, the achievement of long-term survival of most common cancers remains elusive. Multiple factors limit the effectiveness of cancer treatment strategies, including: late disease detection, complex and heterogeneous tumor physiology that necessitates combination regimens, metastasis, natural tissue barriers and solid tumor structures that impede drug penetration, and toxicities that result from exposure of healthy tissues to these therapies. Nanotechnology has the potential to significantly improve upon current cancer therapies through the use of "smart" nanoparticles that specifically address these hurdles**.**

The focus of this Grand Challenge is on the development of novel, multifunctional nano-carriers capable of efficiently transporting diagnostic probes and therapeutic payloads across tissue barriers to specific tumor types. This next generation of carriers will require flexible payload capabilities and highly effective, tumor-specific targeting strategies. The successful development of such a technology platform would enable significant improvements in early cancer detection through tumor-selective delivery of diagnostic probes and imaging agents. The vehicle would also be used to deliver optimized drug combinations directly to the tumor, thereby enhancing therapeutic efficacy and minimizing exposure of healthy tissues.

A 10-year horizon is anticipated for this work. A key early milestone is the selection of cancer type on which to focus. Pending the development of robust tumor targeting strategies, nano-based sensors that significantly increase biomarker detection sensitivity and nanoscale tumor imaging will improve early diagnosis within 5 years. This will enable the development of multifunctional, engineered nanocarriers to deliver drug combinations (drugs, nucleic acids, etc) directly to the tumor. The goal is to deploy a 10-fold more sensitive early detection technology for a major cancer type within 5 years and clinically validate a next-generation nanotechnology medicine delivery system that achieves significant improvement in long term survival in the next 10 years.

Chapter 4. Program Management

Focusing on Grand Challenges

The decentralized nature of the Federal Government's activities in the National Nanotechnology Initiative has motivated PCAST and others to express concern in several reviews, particularly related to setting priorities and coordinating around major themes and opportunities. The enhanced focus on commercialization we argue for in this report reinforces those concerns. Each Federal agency investing in nanotechnology determines its own budget, which is either allocated specifically for nanotechnology or blended within its larger science and technology portfolio. The steering and coordinating bodies of the overarching Federal process – the Nanoscale Science, Engineering, and Technology Subcommittee (NSET) and the National Nanotechnology Coordination Office (NNCO), respectively – are not empowered to make decisions about resource allocations across or within agencies, and the Committee on Technology (COT) in the National Science and Technology Council does not play a leadership role setting common interagency goals and ensuring they are met (Figure 2). NSET convenes agency representatives, but it does not manage agency activities in an integrated way nor create a unified plan within which a specific agency can manage its activities. This loose coupling may have sufficed when the emphasis was on broadening and deepening nanotechnology research, but without a more coordinated approach to commercial transition, the promise of nanotechnology is likely to be left unrealized. The nanotechnology investment by the United States comes at a high opportunity cost when research occurs but no path is available for commercialization.

It is within this landscape that PCAST, as described in the previous chapter, recommends the deployment of Grand Challenges. In addition to the energy it will create in the broad nanotechnology community, we believe the Grand Challenge framework holds substantial potential to enable more explicit and, we believe, more effective leadership and management of NNI 2.0. The specific, common goal of a particular Grand Challenge requires a more active management. By publicly laying out detailed technical and programmatic goals and creating a process in which stakeholders debate and invest in them, defining a Grand Challenge creates a mechanism for an agency, or multiple agencies working in a coordinated, funded fashion, to set priorities. It also helps to ensure that the Federal investment in nanotechnology associated with the Grand Challenge goal becomes a major element of a larger public and private investment and a more productive nanotechnology ecosystem that can support the efficient commercialization of nano-based products. NNI 2.0 leadership thus will not only ensure the introduction of novel nano-based materials, medicines, and technologies but will enhance U.S. competitiveness in a key technology area and lead to infrastructure, capability, and workforce improvements, critical areas of national interest.

Program Management

This section of the report looks at the state of the tools, methods, and responsibilities employed to manage the NNI. Recommendations are made to provide the more active leadership we believe is necessary to successfully transition to NNI 2.0. These recommendations are both enabled by the Grand Challenges process and critical to its success. This theme of more active leadership is not new, and we begin by providing in Table 4 an assessment of the responses to recommendations regarding management and leadership that were made in the 2012 version of this report.

Table 4. Response to 2012 PCAST recommendations on program management.

2012 NNI Review recommendation	Activities in response
The NNCO in partnership with the Office of Science and Technology Policy (OSTP) should work with the agencies to develop agency implementation plans for achieving the goals and objectives outlined in the 2011 NNI strategic plan.	The 2014 NNI Strategic Plan updates and replaces the 2011 Plan and continues "the integrated, interagency approach that informs the nanotechnology-specific strategic plans of the agencies." There is no evidence that the NNCO and OSTP worked directly with NNI agencies to develop formal, agency-specific strategic plans to achieve the NNI objectives, reflecting a preference to defer to agencies for such activity.
Participating agencies should ensure that senior agency officials capable of influencing funding decisions are participating fully and personally in strategic planning activities of the NSET. Officials at this level, in contrast with representatives active at the program or office level, could more effectively drive agency planning and budget allocations to meet NNI strategic directions.	The revised NSET charter stipulates that each agency will appoint one principal representative with the authority to represent the agency. The NSET membership lists in the NNI Budget Supplements, however, show minimal change in NSET representation after the 2012 PCAST recommendation, and the involvement of senior agency officials on the membership list in NSET activities cannot be determined. The revised charter also describes a Senior Steering Group (SSG) that will meet "as needed and at the discretion of the NSET co-chairs." There is no publicly available information to confirm that the SSG has been established or has met.
The Nanotechnology Signature Initiatives should be fully supported in NNI budgets. To this end, PCAST recommends that the Office of Management and Budget increase funding to these Initiatives.	Investment in most Nanotechnology Signature Initiatives, as reported in the annual NNI Supplement to the President's Budget, is essentially flat with the exception of the continued decline in nanoelectronics and robust increase in sensor technology investment (see Table 3). Increased funding had been requested; flat funding in a tight budget environment is consistent with the spirit of the recommendation.

The NSET Subcommittee should create Nanotechnology Signature Initiatives in other priority areas such as homeland security, national defense, and human health.	Launched in 2012, the NSI Nanotechnology for Sensors and Sensors for Nanotechnology: Improving and Protecting Health, Safety, and the Environment is led by the NIH, which reports a $49 million investment. The chemical and biological sensor technologies developed through this NSI have significant applicability to homeland security in addition to health and the environment. The NSI Nanotechnology Knowledge Infrastructure: Enabling National Leadership in Sustainable Design, also launched in 2012, utilizes human-health data in its initial efforts. DOD participates in mission-related aspects of all existing Signature Initiatives.
Appoint the NNCO director as co-chair of the NSET Subcommittee of the NSTC.	The role of the NNCO director is unchanged in the revised charter. The Director continues to manage the NNCO as the secretariat to the NSET Subcommittee and participates in NSET Subcommittee meetings as a committee member but without the policy role implied by NSET co-chairmanship.
Change the requirement that the NNCO director must come from within the Federal Government to allow external, non-Federal experts the opportunity to direct the NNCO.	The revised NSET charter includes the use of the Intergovernmental Personnel Act Mobility Program to staff the NNCO. The new NNCO Deputy Director was hired in 2014 through an Intergovernmental Personnel Act mechanism, which enables temporary appointments to Federal positions from outside of the Federal Government, and the solicitation for the new NNCO Director welcomed applicants from industry and academia as well as Federal agencies.
Create a standing PCAST Nanotechnology Steering Committee of experts from industry, academia, and civil society to provide more frequent and in-depth guidance to the overall initiative and to the Signature Initiatives.	There is no evidence that a standing PCAST Steering Committee or other advisory body is planned.
Dedicate 0.3 percent of NNI funding to the NNCO to ensure the appropriate staffing and budget to effectively develop, monitor, and assess NNI programs.	The revised charter establishes a formula to determine the agency contributions to the NNCO budget. This funding approach is applied to the OMB nanotechnology cross-cut but does not comply with the 0.3 percent recommendation.
Work with the NNCO director to develop a plan for increasing the NNCO budget in line with its new responsibilities.	No new NNCO responsibilities are described in the revised NSET Charter or the 2014 NNI Strategic Plan.

The lack of progress against the 2012 recommendations is telling and disappointing. PCAST's 2012 review of the NNI provided recommendations concerning the leadership roles in NSET to ensure aggressive program management and appropriate representation from the broader government, academic, and commercial community engaged in the NNI. PCAST raised concerns that representatives appointed to the NSET Subcommittee might not have a level of authority within their agencies to influence budget allocations needed to meet NNI objectives.

In aggregate these recommendations aimed to build, within the recognized constraint that the NNI is not centrally funded, an NNI that is more aggressively focused (coordinated strategic plan, Signature Initiatives), more aggressively managed (Signature Initiatives, increased NNCO budget, NNCO as co-chair of NSET), and more broadly connected to the broad nanotechnology ecosystem (higher level agency representation on NSET, enabling NNCO director to be a non-Federal employee, creation of a Nanotechnology Steering Committee).

Building on this assessment from 2012 and with the additional focus on the transition to commercialization and the Grand-Challenges framework, we make a series of recommendations that increase the leadership role played by NSET and the Committee on Technology. We reiterate the concerns identified in 2012 that agency representation in NSET needs to be at a high enough level so that joint decision making can be accomplished and agency plans can be aligned to the direction coming from NSET strategic plan and, more importantly, the Grand Challenges. We find that the Committee on Technology, to which NSET reports, is not actively engaged in helping set and endorse priorities in nanotechnology and we strongly believe this must change. COT must be an integral part of the NNI. Finally, while many of these recommendations are not new, with the transition to NNI 2.0 and its increased focus on support for commercialization, we believe strongly that implementation of these recommendations is critical. If another two years passes without these kinds of changes, we believe the value of a centrally reported NNI will be substantially decreased.

Recommendation 4. NSET should continue to be co-chaired by the Assistant Director, Nanotechnology in OSTP and a representative of one of the participating agencies on a rotating basis. The Assistant Director should ensure that a leader for each active Grand Challenge also participates in a leadership role in NSET. NSET should use Grand Challenges as the primary vehicle for actively managing Federal nanotechnology activities toward directed outcomes

As required by the 21st Century Nanotechnology Research and Development Act of 2003, the National Nanotechnology Advisory Panel has the responsibility to carry out the biennial assessment of the NNI. By Executive Order this activity is housed in PCAST, and we believe this should continue. The 2012 report recommended that a "standing PCAST Nanotechnology Steering Committee of experts from industry, academia, and non-governmental organizations" be created "to provide more frequent and in-depth guidance to the overall initiative and to the signature initiatives."[4] We consider the underlying message of this unimplemented recommendation still to be valid. It is important that a broader set of expert voices from across the nanotechnology ecosystem be added to the conversations and deliberations of NSET, which is comprised solely of agency representatives. This becomes even more important within the context of the Grand Challenges framework as well as the expanded focus on transitioning research breakthroughs to commercial success. Input from industry, technology-transfer experts, and the venture-capital community become critical. We believe that a number of options exist, other than as a standing committee of PCAST, to create a group to provide such guidance and that is separate from PCAST's role in evaluating the NNI.

Finally, while we recognize that legislative action may be difficult at this time, we believe that aligning the separate PCAST review currently every two years and National Research Council (NRC) review currently every three year to the same concurrent three-year time interval can help reduce the burden on the NNCO, NSET, and agencies responsible for providing information.

Recommendation 5. PCAST should continue to carry out the Congressionally-required periodic review of the NNI. Congress should align this review and the triennial National Research Council reviews to the same concurrent three-year time interval to reduce the burden on the Initiative. OSTP, with the support of the NNCO, should create and administer a separate standing committee of cross-sector nanotechnology experts that provides guidance, but does not evaluate, the NNI.

Measurements

The processes and methods employed to measure the progress and return on the Nation's investment are critical to support the direction setting, prioritization, and leadership of the NNI. Evaluation and tracking metrics have been the subject of recommendations in previous biennial reviews, and Table 5 provides an evaluation of the 2012 recommendations and our assessment of actions taken in response.

The Federal Government and the broader nanotechnology community would benefit from more rigorous and publicly available measures of the broad range of activities in the NNI, from discovery research to broad commercial deployment. To this end we provide recommendations for the ongoing research program and for the expanding commercialization activities. We note that these recommendations are also consistent with the Grand Challenge philosophy, which envisions not only clear measurements of ultimate success but also the establishment and tracking of progress to interim recommendations for each Grand Challenge.

Table 5. Response to 2012 PCAST recommendations on measurements.

2012 NNI Review recommendation	**Activities in response**
Agencies should develop a mission-appropriate definition of nanotechnology that enables tracking specific nanotechnology investments supported at the program level. The definition and funding details should be published in agency implementation plans to promote clarity.	NNI agencies utilize the NNI definition of nanotechnology and the Program Component Areas (PCAs) to track their investments and comply with the OMB cross-cut. The 2014 revision of the PCAs was developed, in part, to simplify program and investment tracking. Several organizations, such as the Environmental Protection Agency (EPA), Consumer Product Safety Commission, and the Food and Drug Administration (FDA), have published mission-appropriate context to the definition of nanotechnology to help them carry out their regulatory responsibilities. There is no evidence that these contextual definitions change their investment tracking at the program level.
The NNCO should track the development of metrics for quantifying the Federal nanotechnology portfolio and implement them to assess NNI outputs.	The NSET Subcommittee requested that the NRC provide advice on metrics in its 2013 review of the NNI. The NRC complied, but little responsive activity at the agency or NNI level has been observed. The 2014 Strategic Plan notes that the NNI agencies will continue to monitor metrics development that may be applicable to nanotechnology. No NNCO role in tracking and implementing metrics is evident.

Measurement should capture activities at multiple levels of analysis and different temporal orders. It should also seek to describe the scientific enterprise in multi-level and potentially non-linear terms, not simply in terms of counts or trends but also in terms of complex and often multiple relationships among diverse system components. The current measurement of NNI influence is dominated by counts of publications and patents. This approach, while not unique to the NNI, is flawed for a variety of reasons, including mismeasurement of the process of science, cost, and burden [33] [34, 35]. In particular, patent counts do not measure commercialization or innovation, although they provide useful insights into the areas of activity. Measuring economic impact is much more complex [36][37]. The NSET with the Department of Commerce should begin a process now that will lead to useful measurements of nanotechnology activities to determine how the over $20 billion Federal investment in nanotechnology research has affected the United States economy. Establishing an accurate measurement system is not simple, but other institutions and organizations have already begun these kinds of measurement processes.

Universities and agencies – recognizing the need for accountability – are starting to build people-centered data systems to capture the impact of investments. One example is largely inspired by the project Science and Technology for America's Reinvestment: Measuring the

EffecT of Research on Innovation, Competitiveness, and Science (STAR METRICS) [38]. In that system, data show the building blocks of research at *the project level*: showing the people who do the work and the firms that supply the scientific equipment [39]. The approach minimizes manual, burdensome reporting and uses existing data drawn from the human resource records and financial reports of universities [40]. The data have multiple advantages: they are low-cost, timely, broad-based, high-quality, and extensible. In addition, since they are based on administrative data from payroll and financial records, the source is immediately understandable to stakeholders [41].

This approach provides the foundation for a powerful new data infrastructure that could enable the integration of multiple sources of data and thus permit analysis of the role of funding in stimulating the creation, transmission, and adoption of ideas through those networks. In addition, it is possible to then develop more open and transparent measures of research activity and progress by capturing information on who is supported by research funding; what research is done, with whom and where; and what results flow from that research. We note that a data infrastructure that addresses these science policy goals is also likely to have much broader benefits, for example by enabling research on the sociology of science and by facilitating the navigation of knowledge networks by disciplinary researchers [42]. Appendix I, "Measuring the continuum of the research / translation process and subsequent outcomes using STAR METRICS," provides more details for a possible framework for measuring Federally funded nanotechnology research.

Recommendation 6. NSET, with the Department of Commerce, should execute a process to establish a common set of evaluation metrics to quantify and report the impact on workforce, productivity, and scientific knowledge in nanotechnology for all new research and commercialization programs beginning in FY2016.

Chapter 5. Commercialization

Introduction

Fundamental nanotechnology research over the last decade has yielded an array of technologies that, over the long term, have the potential to transform energy, advanced materials, electronics, medicine, and more. This progress has brought the NNI to a point where the commercial potential that motivated the formation of the Initiative is within grasp. The U.S. nanotechnology enterprise, however, is not optimized to make practical use of nanotechnology advances. NSET and Federal agency leadership should go beyond coordinating basic research to ensuring a robust framework is in place, one that provides researchers who have promising laboratory advances the tools needed to attempt to transform their ideas into products that compete in the marketplace. Attention to commercialization in the nanotechnology community should not come at the expense of basic research; rather, the goal should be the development of a productive nanotechnology ecosystem that commercializes nano-based products through a sustainable pipeline fed by innovative basic research. The achievement of this broad strategic objective will not only ensure the introduction of novel, nano-based materials, medicines, and technologies, but it will enhance U.S. competitiveness and lead to infrastructure, capability, and work-force improvements – all areas of significant national interest.

Through NNI 2.0 the Federal Government should partner with universities, industry, and others to set up that ecosystem and to implement a series of Grand Challenges that set out clear technical goals and generate multi-sector investment in producing transformative competitive products. Chapter 3 described the process of Grand Challenges. This chapter describes the current state of nanotechnology commercialization and summarizes the general technology-transfer process from lab to market. The specific hurdles to nanotechnology commercialization – reproducibly generating nanotechnologies and materials at high volume and addressing environmental, health, and safety (EHS) issues – are coupled with constraints common to all technology development: the skills of the entrepreneur, communication among stakeholders, and availability of capital. These hurdles lead us to three recommendations around manufacturing institutes, entrepreneur training, and forums for multi-sector engagement that are aimed to ensure the ecosystem is in place so that Grand Challenge technologies and other promising nanotechnologies reach the marketplace.

Commercializing Nanotechnology

The 2014 Lux Research report on nanotechnology describes a highly active industry sector in which commercialization of nano-based products continues to increase [22]:

- Revenues from nano-enabled products across all industry sectors grew to $731 billion in 2012.

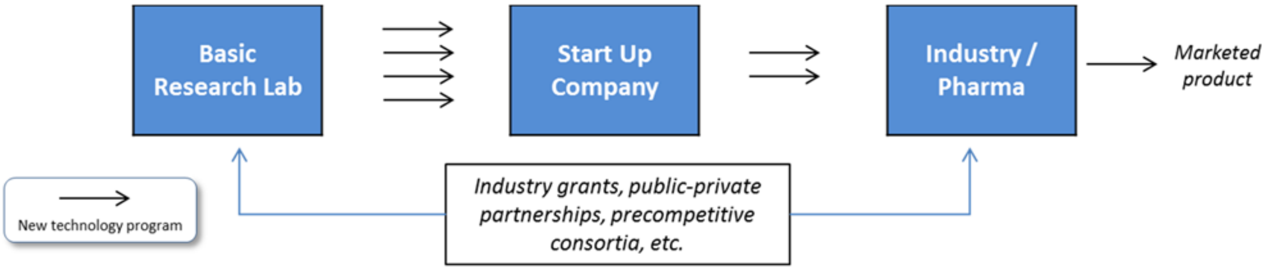
- Total spending on nanotechnology research and development and start-ups by governments, corporations, and venture-capital (VC) investors reached $18.5 billion in 2012, an 8% increase over 2010, with $6.6 billion of this spending from the United States.
- U.S. Federal and State Governments provided $2.1 billion in nanotechnology funding in 2012.
- U.S. corporate spending on nanotechnology increased 19% from 2010 to 2011 and then 11% from 2011 to 2012, amounting to $4.1 billion in 2012.
- United States-based companies received the vast majority of VC investments, capturing 70% (a drop from 89% in 2010) of the $580 million invested in companies developing nanotechnology in 2012. But very few Series-A investments (i.e., the first round of financing after seed capital) made in 2012 were attributed to the nanotechnology category, implying that either investors were focused on their current investments or nanotechnology-infused startups are being more broadly categorized as nanotechnology moves into more broad-based commercialization.

These aggregate numbers suggest that the substantial revenue generated from nano-enabled products and materials is approaching $1 trillion, investments by U.S. corporate and venture capital in commercializing nanotechnologies are relatively modest (approximately $5 billion in 2012). In the absence of metrics that would provide a more quantitative understanding of the nanotechnology ecosystem, it is difficult to draw firm conclusions about how efficiently new technologies are being commercialized, the return on investment in basic research, and whether current funding levels in the commercial sector can maintain a sustainable pipeline of high-value products over the long term.

In addition, these statistics provide little insight into the process, drivers, challenges, and stakeholders involved in moving a promising technology from the research laboratory toward the successful development of a product in the United States. Figure 8 illustrates one possible path that a promising technology might take when it translates from a fundamental technical advance to a marketed product. In the first stage, the academic entrepreneur is the key stakeholder for developing a new technology, and in the next stage, a start-up company might then take on the critical role of refining the promising laboratory discovery, validating its potential to yield useful products, and initiating the product development process [43]. It is important to note that the path as described here and in Figure 8 covers the transition from academic research to the market; other, more nonlinear paths are also common [44-48]. Similarly passages exist for innovation that starts in national laboratories and the basic research laboratories of commercial enterprises.

Federal agencies support entrepreneurs and start-ups through Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) programs, which awarded $110 million in nanotechnology grants across agencies in FY2012 [16]. Public-private partnerships and precompetitive consortia are other mechanisms for enhancing commercialization. Examples include a number of public-private partnerships supported by the

Semiconductor Research Corporation (SRC), which was established in 1982 as a consortium of U.S. semiconductor companies to fund and manage university research [49]. The SRC established the Nanoelectronics Research Initiative in 2005 to bring industry and academic researchers together to develop new electronic-switch technologies that enable substantial improvements in digital performance.



	Academic Research Lab	Start Up Venture	Pharmaceutical Industry
Key Stakeholders	Academic researchers Funding agencies Grant peer-review panels	Academic entrepreneurs Venture capitalists (VCs) Strategic investors (industry venture funds) SBIR/STTR	Technology companies Pharma / large biotech Regulatory agencies (e.g., FDA, EPA)
Ecosystem Constraints	Pursue 'fundable' projects 'White-space' projects may face high funding hurdles Limited view of industry technology gaps & needs Relatively few successful academic entrepreneurs Poor understanding of commercialization process	Strong VC preference to work with established/ successful academic entrepreneurs VCs now favoring later stage funding rounds to advance established companies Start-up funding may be difficult to obtain	Limited view of emerging technologies in academia Pharma relies heavily on biotechs – limited in-house nano activities Seek nanotech solution as a last resort Lack of established EHS standards, practices, and metrics to guide nano commercialization
Infrastructure and Workforce Constraints	Stability of national nanotechnology centers Appreciation for entrepreneurial skills needed to commercialize basic science	Must develop/build fabrication capabilities for early technology development Scale up for advanced testing Cost prohibitive access to some user facilities for proprietary work	Large capital investment may be needed to produce scaled-up quantities for product testing/ validation Nanomanufacturing facilities not readily available GMP facilities must be available early in the clinical development process for drugs. Need to invest before drug enters clinical development Incentive to go outside United States
Funding	Basic research constitutes majority of U.S. nanotechnology spending Numerous agencies fund basic nanotechnology research under the NNI umbrella United States lacks a well-defined nano strategy	VC funding represents a small percentage of the national nanotechnology spending Public funding of nano commercialization projects (e.g., SBIR) cannot fully support nano start-up efforts Industry support for advancing select nano programs through licensing, collaborations, or strategic investments	Industry typically bears the cost of product commercialization, including building the supply chain Build new manufacturing capabilities internally or work with CMOs (United States or abroad)

Figure 8. Commercialization of technology from academic laboratory to the pharmaceutical market.

Constraints Limiting the Commercialization of Nanotechnology in the United States

Although the commercialization model shown in Figure 8 involves well known stakeholders at each stage of the process, a number of constraints inhibit nanotechnology product development. Peer-review of high-risk, high-return ideas, inexperience of first-time entrepreneurs, limited communication among stakeholders, and limited capital for new entrepreneurs are stumbling blocks to commercializing any technology (Box 7). But in nanotechnology, regardless of whether it is a nano-based advanced material, a targeted nanoparticle with a drug payload, or a nano-based diagnostic tracer, generating volumes of nanoscale material in a reliable and consistent manner is required for product testing, validation, and demonstration of scale-up potential for manufacturing.

Alleviating two constraints on nanotechnology commercialization, in particular, could enhance the nanotechnology ecosystem:

- *Investment in nanofabrication facilities* – The commercialization of nanotechnology innovations depends heavily on the successful development of nanofabrication and nanomanufacturing procedures. Few nanomanufacturing user facilities are accessible for developing production procedures, scaling up volumes of nanomaterial for research, or generating commercial supply. In the absence of these facilities, start-ups must assume significant up-front financial risk in developing in-house facilities to support company operations. In addition, the production of nanomedicines for clinical testing and commercial supply must be done in a nanomanufacturing environment that meets the Food and Drug Administration's (FDA) requirements for Good Manufacturing Practice (GMP). Making a significant financial investment in building and qualifying GMP facilities is a considerable risk for a company before the nanomedicine has been assessed for efficacy in human clinical trials to support FDA approval.
- *Comprehensive nanotechnology EHS standards* – Notwithstanding recommendations from previous NNI review panels, no comprehensive EHS standards, best practices, or metrics have yet been established to guide the commercialization and manufacture of nanomaterials. With the continued introduction of nano-based products across industries, some potentially manufactured at a large scale, adequate exploration and quantification of potential risks to safety and the environment and the development of best practices to mitigate any true risks that are identified are needed.

Box 7. General Constraints to Technology Commercialization

- *First-time academic entrepreneurs* – Many faculty members have little training or experience in moving a technical innovation out of the research laboratory into a small company, and the level of support within a university can affect a researcher's ability to spin-off or license a technology. Critical issues related to intellectual property, strategies in acquiring a technology license from the university, forming a company, and acquiring funding all need to be addressed in the early stages of spinning out a start-up company. Unless the new entrepreneur has access to mentors and other resources, promising innovations may not get out of the laboratory.
- *Communication among stakeholders* – Successful academic investigators understand the technical landscape and the potential value of their work, but they may not know how their innovations might address strategic gaps at a large technology company or could be translated into a commercial success. A company R&D director, conversely, might know little about a high-value technology being developed in an academic laboratory. Additional venues are needed to bring together academic entrepreneurs, VCs, industry, relevant Government agencies, and other stakeholders.
- *Venture capital for new entrepreneurs* – Top VCs tend to work with successful academic entrepreneurs with proven track records because VCs perceive these individuals have to lower investment risk. This preference, however, makes fundraising more difficult for the lesser known or less experienced entrepreneur. In addition, the current trend is for VCs to invest in later-stage funding rounds at established companies rather than in early-stage start-ups.
- *Peer review of high-risk, high-return ideas* – Academic investigators pursuing potentially transformative high-risk, high-return projects may find it difficult to obtain funding because of a conservative peer review system. A reviewer may not recommend funding for a proposal because of the perceived risk of the idea or the perception that the work may not align with the granting agency's objectives or risk tolerance.

Of the commercialization constraints specific to nanotechnology – nanofabrication facilities and EHS standards – the first is related to the development of nanomanufacturing in the United States. The latter will be discussed in Chapter 7. A recent Government Accountability Office (GAO) report focused on nanomanufacturing and the effect that nanomanufacturing capabilities have on U.S. competitiveness [7]. The report emphasized that, while the United States remains preeminent in nanotechnology research, it has fallen behind other countries in developing the necessary nanotechnology infrastructure and workforce. The major impediment in this commercial translation typically occurs in the ”Valley of Death” or the

"Missing Middle," the stage where infrastructure is needed between Government-backed research and select privately-funded technology scale ups (Figure 9).

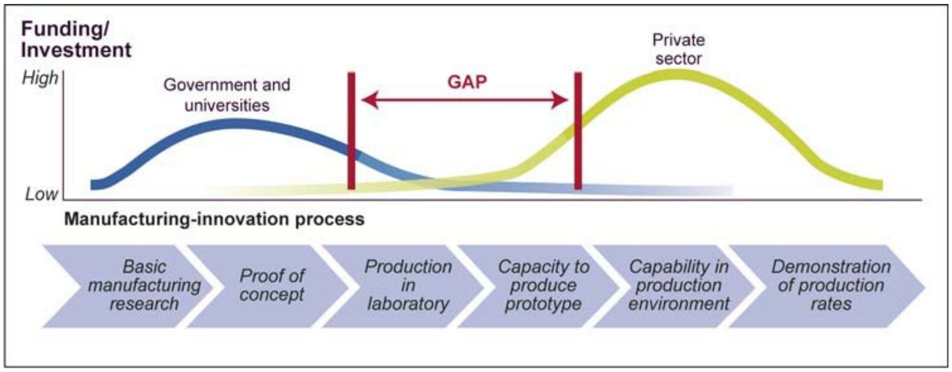


Figure 9. Early stage technology development is typically supported by grants to academic investigators, and late stage private sector investments are made to select technologies with significant potential, leaving a gap in the middle. Figure adapted from GAO report [7].

The United States has lost leadership in several industries to other countries that have emerged as strong manufacturing centers. Semiconductors, advanced batteries for vehicles, and cement-based construction materials, all of which were originally developed in the United States, are now manufactured elsewhere. These examples illustrate how an early competitive advantage in developing high-value technologies can be lost if commercialization is not adequately supported through the development of the necessary manufacturing infrastructure [50-52]. Exciting advances have recently been made in the field of nanomedicine and nanobiology that could enable new approaches to disease treatment, but the United States risks its leadership in this area without a proper ecosystem to support it. Additional details on manufacturing nanomedicine are in Appendix II.

NSET formed the Signature Initiative on Sustainable Nanomanufacturing - Creating the Industries of the Future to spotlight Federal coordination in this area, and in a July 2010 white paper, the Subcommittee describes thrust areas coordinating around the design of scalable and sustainable nanomaterials and processes and around nanomanufacturing measurement technologies, setting out two-year, four-year, and eight-year goals. The FY2014 estimated spending across agencies on nanomanufacturing was $38.4 million, and the FY 2015 budget request is $36.2 million: $6.1 million for National Institute of Standards and Technology (NIST), $0.8 million for Department of Defense, $3.9 million for National Aeronautics and Space Administration (NASA), $23.4 million for National Science Foundation (NSF), and $2.0 million for Department of Agriculture (USDA).

The Department of Health and Human Services, which invested an estimated $469.5 million across all its nanotechnology portfolio in FY2014, estimated no funding for nanomanufacturing in FY2015 but did report the National Cancer Institute (NCI) formed the Translation of Nanotechnology in Cancer consortium to facilitate communication among patient advocates, the Agency, and the pharmaceutical/biotechnology industry and also funded the NCI

Nanotechnology Characterization Lab. The NSF funds four Nano Science and Engineering Research Centers (NSECs) that focus on nanomanufacturing; two centers will retire in 2014 and the other two will retire in 2015 and 2016. The four NSECs in partnership with NIST's Center for Nanoscale Science and Technology, the Center for Integrated Nanotechnologies at Sandia and Los Alamos National Laboratories from the Department of Energy (DOE), and other affiliates together form the National Network for Nanomanufacturing, which organizes an annual nanomanufacturing workshop. In 2014 the USDA began a larger effort to explore the manufacture of nanocellulose materials.

While each agency considers areas of nanotechnology interest according to its mission, the challenges in manufacturing are likely to impede commercializing advanced nanomaterials, nanomedicine, and other nanotechnologies unless the Federal Government addresses the valley of death, which involves the need for nanofabrication facilities to create high volumes of nanotechnology product. Engaging the broad manufacturing initiative established by the Obama Administration is a promising approach.

Manufacturing Innovation Institutes Dedicated to Key Nanoscience Areas

In 2012 and building on past PCAST recommendations, the Administration announced plans to create a National Network for Manufacturing Innovation (NNMI) "consisting of regional hubs that will accelerate development and adoption of cutting-edge manufacturing technologies for making new, globally competitive products." These hubs, called Manufacturing Innovation Institutes (MIIs), are intended to strengthen U.S. competitiveness, initiate new ventures, and boost local and state economies – with the broad strategic goal of innovating and scaling up advanced manufacturing technologies and processes [53]. Importantly, the institutes are to be industry-led. They will require strong partnerships among industry (companies large and small, established and start-up), academia, non-profit organizations, and states, with the aim of investing in and accelerating the development of cutting-edge manufacturing technologies.

To date four MII's have been established and a fifth in competition [54]. In both his 2013 and 2014 State of the Union addresses, the President asked Congress to authorize a $1 billion investment to create a network of up to 15 regional MMIs. The NNMI initiative has significant potential to address a critical challenge now being faced by companies trying to advance nano-based products, nanomedicines, and advanced nanomaterials.

Chapter 3 outlined the characteristics and best practice processes to choose a Grand Challenge. Given the strong worldwide competition to achieve the best nanomanufacturing capabilities, we believe at least one of the first Grand Challenge selected should be mature enough to take on manufacturing challenges as the results will be needed to achieve almost any Grand Challenge that comes after it. And we believe a good place to start is to leverage the current Manufacturing Innovation Institutes that have been created under NNMI.

Recommendation 7. NSET should work with Federal agencies to define potential Manufacturing Innovation Institutes dedicated to nanoscience and nanotechnology as part of the National Network for Manufacturing Innovation program.

I-Corps Training for New Entrepreneurs

Another constraint on commercialization, which is common to many technology areas, is that training for a scientific or engineering career typically does not provide a working knowledge of finding start-up funding, obtaining technology rights, developing a business strategy, and running a company, all skills helpful if not essential for moving high-value technologies out of the research lab. To begin to address this situation, the National Science Foundation introduced the NSF Innovation Corps (I-Corps) program. Its goal is to prepare scientists and engineers to "extend their focus beyond the laboratory and broadens the impact of select, NSF-funded, basic-research projects." I-Corps Teams are composed of academic researchers, student entrepreneurs, and business mentors who pursue a curriculum that provides real-world, hands-on learning about what it takes to successfully translate fundamental technical advancements into commercial products [55].

Importantly, the I-Corps program is not just training but intends to foster entrepreneurship that directly leads to the commercialization of a technology that has been supported previously by NSF-funded research. Program-commercialization activities will most often focus on start-ups founded by the I-Corps participants; successful I-Corps projects are ready to form businesses. The NSF SBIR and STTR programs are important vehicles for launching those businesses.

Currently only NSF grant awardees can apply to participate in I-Corps, but we see strong value in expanding this program across other funding agencies (e.g., National Institutes of Health {NIH} and the Department of Energy) and significantly enhancing the innovation landscape across technology sectors, including nanotechnology. PCAST supported the development of the I-Corps program in our 2012 report, *Transformation and Opportunity: The Future of the U.S. Research Enterprise* [56]. Only a few of the nearly 300 NSF I-Corps grantees have been working on nanotechnology projects. The NSET and agencies could work with NSF to support an I-Corps hub in nanotechnology that accepts teams funded from any agency on successful nanotechnology projects.

Recommendation 8. The NSF, in consultation with NSET, should expand the NSF Innovation Corps to include a specific focus on entrepreneurship in the nanotechnology area, and NSET, NIH, and DOE should leverage this program concept to make it available to a broad range of scientists working in nanoscience and technology.

Robust Communication across the Nanotechnology Ecosystem

As occurs in many industries, poor communication among stakeholders impedes the ecosystem for nanotechnology commercialization. As discussed above, the new academic entrepreneur may not know technology gaps that large technology or pharmaceutical companies face, and companies likely do not know the value of new scientific findings from academic laboratories. Some venture-capital fund managers might prefer to work with established investigators who are experienced entrepreneurs because they decrease the investment risk, while the lesser-known, new entrepreneur may have a difficult time accessing funding for an innovative finding.

To address some of these issues, organizers of a variety of national scientific meetings have established partnering sessions for academic investigators, start-ups, and large companies to explore their mutual interests during major meetings. The National SBIR/STTR Conference is one avenue that crosses technology areas. Providing these partnering meeting opportunities at appropriate national meetings with nanotechnology interests could enhance the nano ecosystem in ways that further enable the commercialization of nanotechnology products. The annual Nanotechnology Conference and Expo, most recently as Nanotech 2014 organized by the Nano Science and Technology Institute, begins to address some of these communication gaps. It began in 1998 and is now co-located with several other industry-specific technology innovation expos. The annual Nano Technology for Defense conference hosts partnering meetings for those in the defense industry. With new entrepreneurs in nanotechnology arising from many different disciplinary fields, evaluating whether additional partnering sessions at disciplinary- or industry-specific conferences would be valuable. The Department of Commerce should leverage its experience with other technology industries and the support of the National Nanotechnology Coordinating Office to create a regular economic-development forum that focuses on commercial development. With nanotechnology research alive in so many different fields, the nanotechnology community should ask what additional measures are needed to fully engage the range of stakeholders toward any one nanotechnology Grand Challenge.

Along similar lines, information about nanomaterials could bring commercial and research activities together. Already NanoHUB.org provides online tools for researchers and more to teach, learn, and collaborate around nanotechnology, and the Nanomaterial Registry curates data about nanomaterials' interaction with biology and the environment. Establishing a *'clearing house' for information* related to the general nature of nanomaterials disclosed to be in the development process (non-proprietary information) could create a resource for exploring available nanotechnology solutions to key technical problems being faced across various industries. Assessing how to communicate effectively with industry with a focus on identifying opportunities and fostering technology translation will be important in NNI2.0.

Finally, a key limitation that the nanotechnology ecosystem suffers from is the current inability to measure accurately the economic impact that nanotechnology commercialization has had. Nanotechnology has had a significant impact on multiple industry sectors; the role that nanotechnology has played, however, is not always obvious and the development of robust metrics that quantify the commercial impact of nanotechnology could provide strong support for continued investment in this key technology area and highlight areas that should be supported in the future.

Recommendation 9. The NNCO and the Department of Commerce should establish an annual nano-focused economic-development forum designed to bring together academic researchers, the venture capital community, biotechnology, and other industry in a format that enhances the possibility to create business partnerships.

Identify and Incentivize University, Local, State, and Regional Best Practices that Encourage Technology Commercialization

Training in business skills and development will help first-time academic entrepreneurs, but the resources available to a first-time academic entrepreneur within her/his own university or institute may equally affect whether a research advance leaves the laboratory. The resources and culture for commercializing research vary significantly across U.S. universities and national laboratories. Patenting and technology transfer cannot take place without institutional support. The institution plays a critical role in guiding the patent application process, providing funding for the costly prosecution of patent applications and enabling the licensing of technologies to outside parties. Institutional support for technology translation can be enhanced through university administrations placing a strong focus on patenting important findings of their researchers, by facilitating technology and material transfer among collaborators, and establishing business development offices [57]. Due to the high cost and time involved, researchers often publish their work without filing strong patent applications [58]. In doing this they run the risk of losing exclusive access to their own technology, making it very difficult for them to commercialize, although potentially creating positive effects on the market as a whole [59]. VCs, strategic investors, and large companies are unlikely to invest in technologies that do not have a strong proprietary intellectual property position. By providing modest funding and legal assistance, the home institution can significantly lower the barrier to patent filing and significantly increase the probability that the technology can ultimately achieve strong patent protection.

Among the universities with active technology transfer offices, the range of support likely varies widely. Building upon the National Research Council study *Managing University Intellectual Property in the Public Interest*, an appropriate expert group potentially supported in part by the NNI agencies should survey a range of institutions that have been successful in encouraging technology transfer to the private sector to determine best practices in the following areas: (i) amount spent on tech transfer per $100 million in research dollars; (ii) number of technology transfer staff per $100 million in research dollars; (iii) conflict-of-interest management; and (iv) responsibility of researchers in submitting disclosures [60]. This information may lead to a more efficient use of Federal funding that could result in the enhanced translation of NNI funded research. The survey should also explore practices that universities and national laboratories have in place regarding the publication of key data prior to filing the appropriate patent applications. NNI agencies should also design and implement a plan that motivates a stronger emphasis on the commercialization of relevant technologies that emerge from institutions involved in Federally funded research.

In addition to support at universities, State and regional activities have fostered nanotechnology commercialization. Regional, State, and local nanotechnology initiatives have existed in at least 24 States to provide resources and facilitate collaboration between the private sector and academic researchers. These initiatives were supported with combined funding from Federal, state, local, and private partnerships. Due to the youth and volatility of nanotechnology research in conjunction with high-risk business models, most of the initiatives have diminished or completely shut down because of their inability to retain strong Federal and State support, especially through the recession [61]. The continued influence of initiatives that have ended suggest that the sustainability of nanotechnology initiatives may be less important than their ability to have an immediate impact on the prevailing state of nanotechnology research. While many initiatives have come to a close, thriving start-up and small and medium enterprises have been built as a result of the programs [62].

We note two specific examples. The Oregon Nanoscience and Microtechnology Institute (ONAMI) is a State government investment model that supports researchers and small businesses by encouraging collaborative research with matching grants, supporting access to shared laboratory spaces, and offering funding and expertise for commercialization. Since its inception in 2004, ONAMI has helped produce 32 startup companies and 61 patents. The Arizona Nanotechnology Cluster is an example of a volunteer and local business funded initiative. Since 2003, the Arizona Nanotechnology Cluster has provided seminars, networking, and educational opportunities, and has served a voice for Arizona nanotechnology in local, State, and national government. The Cluster partners with State research universities and nanotechnology businesses to increase the role of nanotechnology in the Arizona economy.

Chapter 6. The NNI Research Enterprise

Introduction

In NNI 2.0, Federal agencies, NSET, and the NNCO need to focus on setting up platforms from which nanotechnology can launch into commercial products, but as those efforts build, continued support of the research enterprise must ensure that discovery and exploratory research remains vibrant. As the NNI matures, achieving Grand Challenges will require a balanced portfolio of activities by the NSET and Federal agencies in discovery, exploration, and commercialization that will enable the United States to simultaneously reap the benefits of past NNI investments and discoveries, while ensuring that it is planting the seeds of discovery that can be harvested indefinitely into the future. *Without discovery research now, there will be nothing to commercialize in the future.*

The investments of the National Nanotechnology Initiative have already yielded tremendous nanoscale science in the United States. The first 10 years of the NNI was a period when researchers built the nanoscience foundation for technology – creating, studying, and understanding new classes of nanoscale building blocks. In the next phase of research, the goal is to build on that foundation by controlling the structure of those building blocks reproducibly and at the atomic scale, by moving from passive to active nanostructures, and by integrating nanoscale elements into complex assemblies with emergent and, ultimately, predictable properties. The understanding required to bring these to fruition under NNI 2.0 will be critical to solving many of the major scientific mysteries and societal challenges facing the United States. Achieving this control, function, and integration, however, is more difficult than the creation of the nanoscale units themselves. As in the path to electronics, the discovery of the transistor was only the first step in a long journey to laptops, smartphones, and the Internet.

The path from discovery to innovation has three distinct phases, as shown in Figure 10: discovery, exploration, and commercialization. Each stage requires different resources and focus, but all three are essential. This chapter focuses on actions to support the first two steps, discovery and subsequent exploration.

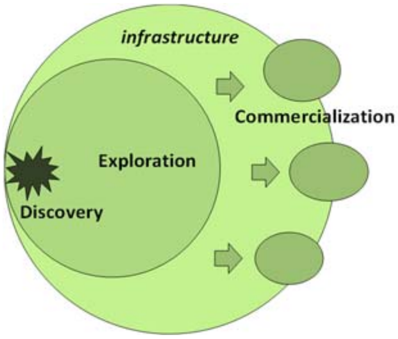


Figure 10. The stages of technology development begin with basic research discovery (inner star). In the discovery phase, new science or technology happens and high-risk, high-reward activities occur. During the exploration of these discoveries (medium green circle), their implications are investigated and their potential impact can begin to be assessed. Finally, with the support of infrastructure (light green circle), commercialization stage occurs when the discovery is incorporated into commercial applications (dark green circles).

Major research breakthroughs are needed during NNI 2.0, including:

- Atomic scale control – new approaches to create complex nanostructures with the atomic-scale precision of their biological equivalents.
- Active nanostructures – creating nanostructures that are active, i.e., perform a complex physical, chemical, or electronic function.
- Integration and emergence in nanoscale assemblies – creating assemblies of nanostructures whose behavior emerges from the collective and is not straightforwardly predicted from the behavior of the individual constituents.

PCAST believes that the most successful approach to achieving these goals is to focus on not just what but *how* interdisciplinary science gets done during discovery and exploration. In particular, the recommendations for the *discovery* phase will empower **people** to do their most creative work to generate new breakthroughs, and recommendations for the *exploration* phase will **focus** the efforts of large groups on specific objectives as the goals become clear. Federal agencies should continue to support fundamental research in nanoscience and nanotechnology.

Investing in Creative, High-Risk Research Through Single Investigators

New ideas and paradigms emerge when creative minds are given free rein to explore. By definition, breakthroughs cannot be anticipated in detail or planned in advance, but creating the right environment allows them to flourish. And new ideas are the seeds from which future technologies grow. Despite this case, a crisis is growing in American nanoscience: top researchers are leaving the United States for senior positions around the world [63] [64]. Researchers are leaving because of the challenge in obtaining flexible, long-term funding that supports their ability to generate and sustain their most creative ideas. Stopping this trend is essential. The cultivation of top researchers and their creative ideas cannot be neglected without severely damaging the long term prospects of nanotechnology leadership by the United States.

We believe that the best way to foster discovery is to identify the country's most talented people and empower them to explore their vision. Providing highly skilled and talented people with the resources to take risks and explore new directions needs to occur at every stage of the science and technology researcher's career: at the graduate level, at the new faculty level, and at the senior faculty level. The Federal Government supports a number of fellowship programs for graduate students, and programs such as the Young Investigator Programs by the Office of Naval Research, the Army Research Office, and the Air Force Office of Scientific Research and the Presidential Early Career Award for Scientists and Engineering by the National Science Foundation (NSF) support new faculty. Private foundations grant awards such as the Packard Fellowships and Sloan Fellowships to new faculty as well.

These types of support launch new faculty careers, and equally important, they encourage risk-taking and discovery at what is often the most creative and paradigm-shifting stage of a researcher's career. New faculty have new ideas, and empowering them at this stage to explore their scientific vision is a powerful force for change and for breakthrough discovery. PCAST encourages the NSET agencies to continue to provide strong research support to outstanding early career researchers in nanoscience and technology to pursue what the researchers consider to be the most promising avenues of research.

For senior researchers, the story is different. Top researchers in the United States are leaving for either Europe or Asia because they cannot secure long-term, stable funding in the United States for their most visionary work. The U.S. funding system is fragmented among agencies beholden to individual missions and is captive to the peer-review system that not only appropriately weeds out the inferior ideas but also potentially dismisses truly revolutionary ones. This perfect storm makes it nearly impossible for a faculty member to invest the time and effort both to obtain grants that support a significant research group and to pursue her or his most creative, high-risk ideas. Nanoscience and technology is receiving world-wide interest and research investment, yet even the very best researchers suffer from the vagaries of funding that limit their creativity, productivity, and ability to pursue the most promising, but high-risk, areas of nanoscience and technology research. This uncertainty in raising funding is eroding U.S. competitiveness in retaining the best scientists in the world.

European and Asian competitors offer very attractive positions to address the needs of top, senior researchers. Positions such as the Max Planck Institute Directorships in Germany or the ERC Pioneer Program in Europe provide a strong, consistent base of funding that allows the best researchers to explore high-risk, high-reward science. The United States needs funding opportunities to support the Nation's best and most productive researchers in a steady and substantial manner that allows them to concentrate on developing creative ideas. A model is the National Security Science and Engineering Faculty Fellowship (NSSEFF) program at the Department of Defense (DOD). This highly competitive program supports faculty with approximately $3 million over five years to do cutting-edge science that has significant national security implications. The National Institutes of Health (NIH) similarly awards highly competitive Pioneer Awards at $500,000 per year for five years for high-risk research by a single investigator at any stage in their faculty career.

We propose a Nanoscience Faculty Fellowship Program modeled on the NSSEFF or as an extension of that program to support the most innovative and creative researchers in nanotechnology. These researchers will also serve as a valuable pool that could be tapped for oversight, review, advice, and management of the NNI portfolio in a manner similar to what occurs with the NSSEFF for national security issues. Approximately five substantial awards per year that each last five years would result in steady-state support for 25 nanoscience researchers. We believe this is a highly effective means to support creative, high-risk research, enabling highly talented and productive researchers to pursue work not likely to be funded by traditional mechanisms and encourage them to stay in the United States.

Recommendation 10. Recognizing growing international funding competition that is attracting U.S.-based talent to go abroad, NNI agencies should substantially support the best single investigators to pursue creative, high-risk research. In particular, the NSF, DOE, DOD, and NIH should coordinate to ensure that at least five new National Security Science and Engineering Faculty Fellowship (NSSEFF)-style senior investigator grants in nanoscience and nanotechnology are funded per year.

Exploratory Research Through Research Centers

Achieving some Grand Challenges in nanotechnology will require transdisciplinary, exploratory research, and Federal agencies can catalyze that exploration by investing in research centers. Centers can be teams of co-funded investigators collaborating on a common research vision using investigators' own labs – either at one institution or distributed across many. Centers can also be critical physical laboratories that provide the proper research infrastructure and expertise for nanotechnology science and technology that are essential components of the NNI mission. Centers in either case provide the research environment and the training of next generation scientists and engineers who are needed to achieve Grand Challenges.

Transdisciplinary Research

Federal agencies support a range of research centers that can be forums of collaboration for transdisciplinary research in nanoscience. National Cancer Institute's (NCI) Centers for Cancer Nanotechnology Excellence and NSF's Nanoscale Science and Engineering Centers focus on nanotechnology alone while NSF's Engineering Research Centers, DOD's Multidisciplinary University Research Initiative, DOE's Energy Frontier Research Centers, and NSF's Materials Research Science and Engineering Centers are successful programs with broad portfolios that support nanotechnology research. Nanotechnology-focused centers can also be as large as NSF

Science and Technology Centers or DOE Energy Innovation Hubs. We believe research centers are critical for the exploratory research that will translate discovery research into technology.

While research centers offer myriad potential benefits, they have key risks. In particular, the cost of funding unfruitful research is much greater in a multi-investigator research center than in an individual investigator award. If the research of a single investigator is unsuccessful, a considerably smaller amount of funds are lost in comparison to the failure of a center to produce. One way to mitigate this risk is to ensure that each center has strong leadership that will be able to guide its path away from unrewarding efforts, toward meaningful and productive research. Ensuring strong leadership at the helm of centers may be done in several ways. One technique used by the DOE in managing the Energy Frontier Research Center program is to embed a management review after the first year of a center's funding. A mechanism DOD employs in centers is to utilize pilot grants for centers, whereby continued funding is contingent on a strong start in the first year of the center.

Another pitfall of center-based research is the potential to stifle innovation inadvertently through an overly rigid structure of reporting and requirements. To avoid this, agencies could outline broad goals for a successful center rather than a strict framework of research requirements. This will allow ideas to "bubble up" from investigators and allow researchers to pivot from one project to another should an unexpected, promising discovery be made.

In order to maintain the health of a research center ecosystem, centers should have built-in checks and balances to ensure progress is still being made. This will allow agencies to shut down unproductive centers that repeatedly fail to meet goals while continuously funding centers that are doing well, regardless of an arbitrary granting timeline.

Center-based grants are an important part of the any research portfolio, especially in nanoscience and nanotechnology. To train students who can think critically about the problems facing society today, especially in the realms of nanoscience and nanotechnology, program managers and faculty must find ways to overcome disciplinary constructs to train a new type of scientist: one who is not only "multilingual" across multiple scientific fields, but who can speak a common language and foster communication and collaboration among many disciplines.

The Grand Challenges discussed in Chapter 3 will be a powerful focal point for exploratory research. We propose that the Federal agencies support a program of nanoscale-focused research centers. One example could be a center supported by NSF, DOE, and National Institute of Standards and Technology (NIST) as a Particle Foundry, which would provide the research community a unique educational and training resource for the manufacture and production of nanoparticles by batch, continuous, or microfluidic methodologies. Additional nanoscale-focused research centers may be supported by a single agency or in a joint effort by several agencies, but these nanoscale science and engineering centers should be funded at least 50% by a single directorate or agency that functions as its disciplinary home. As an exemplar for the type of centers to be established, agencies can look to the NCI and its robust Alliance for Nanotechnology in Cancer initiative, including the Nanotechnology Characterization Laboratory. Further value can be added using this model even within the NIH by instituting a center program analogous to the NCI to address disease indications other than cancer including autoimmune diseases, infectious diseases, and more.

Infrastructure

DOE's Nanoscale Science Research Centers, NCI's Nanotechnology Characterization Laboratory, NIST's Center for Nanoscale Science & Technology, and NSF's National Nanotechnology Infrastructure Network (NNIN) provide essential infrastructure for nanotechnology discovery and exploration. They provide ready access to specialized tools that are generally too expensive for each laboratory, institution, or company to acquire. They provide essential training in interdisciplinary nanoscale approaches and techniques to new generations of researchers, industrial engineers, and entrepreneurs.

The NNIN is a network of 14 university-based user facilities that provide open-access tools and resources to nanotechnology researchers in universities, industry, and Government. Established in 2004 through a 10-year NSF grant awarding a total of $179.8 million, the NNIN provides over 1100 advanced instruments at affordable costs to "enable rapid advancements in nanoscale science, technology, and engineering."[65] The NNIN also maintains educational and outreach opportunities through initiatives such as the Research Experience for Undergraduates program.

With the original NNIN set to expire in 2014, the NSF is developing a successor program in FY2015. As the existing infrastructure retires and the agency begins a new program, providing open access, accessible facilities that reach a very wide audience in a cost-effective manner, both in the public and private sectors will be critical. The retiring NNIN labs are strongly leveraged, with NNIN funding only a small, but key, part of the overall budget. In particular, the NNIN funding helps to link facilities across the country together and keep them open to outside users. Without the NNIN funding, many of these facilities likely would be significantly less accommodating to outside users, and in case of the smaller participants, might no longer be viable at all.

Recommendation 11. NSF, NIH, DOE, DOD, and NIST should strongly support nanoscale research centers and infrastructure networks to ensure the effective training of a new generation of transdisciplinary scientists and engineers, in particular by strongly supporting the Next-Generation National Nanotechnology Infrastructure Network.

Chapter 7. Environmental, Health, and Safety Issues

Introduction

PCAST's *Fourth Assessment of the National Nanotechnology Initiative* lauded the "significant progress" made by the NNI to address potential environmental, health, and safety (EHS) risks of nanotechnology [4]. It noted the rapid growth of research funding for nanotechnology EHS issues, the implementation of PCAST's earlier recommendation to identify a central coordinator for EHS-research within the NNCO, and the expansion of the Nanotechnology Environmental and Health Implications (NEHI) Working Group charter to address cross-agency nanotechnology related policy issues. The fourth assessment praised the development and release of an EHS research strategy that incorporates nanomaterial measurement capabilities, human exposure assessment, human health, environment, risk assessment, risk management, and predictive modeling and informatics. It also called out significant NNI progress in addressing the potential EHS risks of nanotechnology, noting the development and release of a national EHS research strategy and articulating an approach that incorporates the "evolving research needs and the strategic research plans of three relevant agencies."

While we noted that there was good agreement between the NNI strategy and the findings of the 2012 National Research Council (NRC) report *A Research Strategy for Environmental, Health, and Safety Aspects of Engineered Nanomaterials*, we also expressed concern about the "lack of integration between nanotechnology related EHS research funded through the NNI and the kind of information policymakers need to effectively manage potential risks from nanomaterials." [66] This integration is important to promote commercialization and obtain regulatory approval for products to reach the marketplace. This sentiment was echoed by the 2014 NRC report *Research Progress on Environmental Health and Safety Aspects of Engineered Nanomaterials*, which concluded that risk characterization by engineered nanomaterials (ENMs) "across their life cycles is a scientific challenge that requires integrated, quantitative and systems-level scientific approaches." [67] The latter report includes a detailed outline of the research progress since 2012, classifying the progress as substantial, moderate, or minimal. In this assessment, we will focus our recommendations on the integration of knowledge and research to improve regulatory decision making and commercialization of nanotechnology with the acceptance, trust, and support of the public.

Review of 2012 PCAST Recommendations

Table 6 shows a summary of the recommendations made in our 2012 NNI review along with an assessment of actions taken against those recommendations. We find good alignment and progress between the recommendations and the actions.

Table 6. Response to 2012 PCAST recommendations on environmental, health, and safety issues.

2012 NNI Review recommendation	Activities in response
Establish high level, cross-agency authoritative and accountable governance of Federal nanotechnology related EHS research so that the knowledge created as a result of Federal investments can better inform policy makers.	The NSET NEHI Working Group remains a very active and collaborative cross-agency forum that released a review of NNI EHS research activities, accomplishments, and collaborations, *Progress Review on the Coordinated Implementation of the NNI 2011 EHS Research Strategy* (June 2014). Several NEHI agencies also participate in the Emerging Technologies Interagency Policy Committee Nanotechnology Working Group and provide information on their research activities directly to policy makers.
Increase investment in cross-cutting areas of EHS that promote knowledge transfer such as informatics, partnerships, and instrumentation development.	The Nanotechnology Signature Initiative (NSI) on Nanotechnology Knowledge Infrastructure will provide tools and empower research communities to translate EHS data to information and knowledge. Investment in this NSI jumped from $7.2 million (actuals, FY2013) to $32.1 million (estimate, FY2014) and $26.2 million (request, FY2015). No investment breakdown for partnerships and instrumentation is available. The EHS budget remains steady at $115 million (actuals, FY2013), $113 million (estimate, FY2014) and dips slightly to $112 million (requested, FY2015). These figures include instrumentation and partnership activities. Partnership activities, defined as Centers and Networks, are identified in the NNI EHS Progress Review, Appendix C.

Current Status of Nanotechnology EHS

The current status of nanotechnology EHS is characterized by (i) a reliance on hazard and risk analysis on a case-by case basis in spite of the rapid expansion of the technology; (ii) a paucity of exposure, dosimetry, and lifecycle data because of the lack of information about materials in the commercial chain, as well as slow emergence of the instrumentation required to detect ENM exposure under complex biological and environmental conditions; (iii) continued reliance on descriptive (non-mechanistic) animal studies (often poorly integrated with cellular and *in vitro* data) for regulatory decision making; and (iv) regulations based on ENMs as novel chemical substances which, by way of new use rules and pre-manufacturing notices, negotiate access to marketplace without a coordinated approach between Government agencies, industry, and academia [68]. At the same time, it is also characterized by (v) the emergence of mechanistic and systems-level approaches to assess ENM safety, instead of just relying only on outdated chemical toxicology study methods and (vi) a growing awareness of the potential utility of alternative test strategies. These strategies decrease animal use and speed up the rate of discovery and knowledge generation by relying on more quantitative, mechanistic, and systems-level approaches that involve high throughput screening, computational modeling, and a variety of decision analysis approaches to improve regulatory decision-making [69].

While a variety of reasons explain why knowledge gathering and research cannot, as yet, address all the information requirements for hazard, exposure, dosimetry, and lifecycle analysis, there is a clear need to integrate and use available knowledge for safety assessment, decision analysis, and regulatory approval in light of the increasing number of products making their way to the marketplace. At the same time, the remaining knowledge gaps called out in the 2012 and 2014 NRC reports need to be addressed by well-planned and judicious research as well as obtaining information about the fate and lifecycle of nanomaterials entering the value-chain [66, 67]. Focusing academia, industry, and the Federal Government together on leading industry sectors relying on nanotechnology is important to develop transparency and consensus on the nanotechnology EHS decision-making process that is required for safe implementation.

To continue reducing nanotechnology EHS uncertainty, expedite nanotechnology commercialization, and safe implementation of nanotechnology, the Environmental Protection Agency, National Institutes of Health, National Institute for Occupational Safety and Health, Food and Drug Administration, National Science Foundation, and National Institute of Standards and Technology should play a key coordinating role in (i) establishing multi-stakeholder Government, industrial, and academic communities that focus on nanotechnology EHS decision analysis in key commercial sectors dependent on ENM access to the marketplace and in (ii) integrated decision analysis, based on current available (but incomplete) data and information, while continuing to oversee the development and implementation of measurement tools for new and actionable data collection to improve the level of certainty and regulatory decision making.

In addition, to improve hazard and risk assessment, the nanotechnology community, together with appropriate regulatory authorities, should investigate how more rapid mechanistic approaches based on nanomaterial properties and interactions at the nanotechnology-biology interface can be used to replace chemical-oriented hazard assessment by tiered risk assessment approaches. Some of this testing should involve high throughput screening and computational analysis to speed up hazard ranking and establish predictive principles for toxicological analysis and safer design. The tiered risk assessment approaches should include both qualitative (e.g., listing of evidence, best professional judgment, weight of evidence, control banding, ENM categorization) and quantitative (e.g., occupational exposure limits, quantitative structure-activity relationships) measures to allow early as well as more advanced decision analysis, each of which has a role to play in deciding whether an ENM is a “material of concern” and/or how much additional testing is required to reach a decision on safe implementation [70].

To obtain more information about exposure in humans and the environment, the 2012 PCAST recommendation of "the importance of a life cycle approach to assessing risks" is still highly applicable, but its implementation by the lack of information about the volumes and types of materials in the commercial value chain. This outcome reflects, in part, the reluctance of industry to disclose information because of the uncertainty in regulatory decision-making and the fear of disclosing confidential business information. While France is attempting to solve this through a national nanomaterial registry, it is uncertain whether such an approach will succeed in the United States [71]. Thus, improving the ability to perform integrated decision analysis under the coordination of NNI becomes even more important to reduce uncertainty.

The Federal Government, with the assistance of industry, also needs to intensify research efforts to improve the instrumentation for assessing exposure and performing dosimetry analysis in humans and the natural environment (including potentially sensitive terrestrial, aquatic, estuarine and marine ecosystems, wastewater treatment systems, and end-of-life disposal sites). Lifecycle analysis and knowledge of materials in the value chain are also important for early and cost-effective decision analysis about the possible target sites to focus on.

Activities such as those described previously presuppose a competent multi-disciplinary workforce. This workforce must continuously upgrade and improve its nanotechnology EHS expertise toward developing sustainable technologies and obtaining public trust and approval. The $121.1 million in nanotechnology EHS funding requested for FY2014 does not include funding for nanotechnology EHS test facilities where academia, industry, and Government can engage in EHS assessment and safer design of marketable products in the same way as the National Cancer Institute's Nanotechnology Cancer Laboratory is undertaking to foster cancer nanotherapeutics [72]. Some of the larger multi-disciplinary nanotechnology safety centers funded by NSF will sunset in 4 years, at which point no comprehensive, multidisciplinary communities will exist to continue the integrated research and education that is needed to continue to develop a U.S. nanotechnology EHS workforce.

Addressing the ethical, legal, and societal implications (ELSI) of nanotechnology in a proactive manner is critical to ensure public trust, especially in an era when the translation of critical research performed under NNI will lead to increased commercialization of nanotechnology [73]. NNI should continue to engage a variety of ELSI experts to gauge the societal impact, understanding, and perception of the added value of and concerns about nanotechnology. To increase stakeholder awareness and education concerning ELSI issues, appropriate and relevant ELSI information about the efforts to improve nanosafety should be disseminated. In addition to informing the public, the participation of members of the public in multi-stakeholder communities is critical.

Recommendation 12. NSET should continue to support the development of a multidisciplinary nanotechnology-EHS ecosystem that promotes non-animal based (alternative) test strategies for safety assessment and multi-stakeholder participation in regulatory decision-making and safe implementation to facilitate market access of nanomaterials and nanotechnology-enabled products by

a) Establishing multi-stakeholder working groups (e.g., semiconductors, carbon nanotubes and grapheme, silica) in which academia, industry, and Government experts use evidence-based nanotechnology EHS safety and risk analysis to facilitate the commercialization and entry of these materials and products to the marketplace;
b) Promoting the use of cost-effective rapid-throughput screening and mechanistic, predictive, and tiered risk assessment approaches that address the areas of greatest nanotechnology EHS concern and uncertainty;
c) Advocating for long-term and stable funding for nanotechnology EHS research, workforce development, knowledge acquisition, benign design, and nanotechnology EHS test facilities; and
d) Fostering the development of decision analysis methods and tools that make use of current knowledge for regulatory decision-making, while actively promoting actionable hazard, exposure, risk, and lifecycle analysis.

Appendix I. Measuring the Continuum of the Research/Translation Process and Subsequent Outcomes Using STAR METRICS

Any attempt to create a data infrastructure around the effects of research and development (R&D) must confront the fact that relevant data (e.g., funding agency R&D awards, educational institution outcome data, research publications) are currently drawn from disparate sources, using widely differing methodologies and approaches. Thus, building a coherent data infrastructure is particularly challenging. Inputs, outputs, and outcomes are not currently generated or combined in a systematic fashion. The development of consistent and reliable answers to stakeholder requests requires the use of common data sources and standardized methodologies for data cleaning and analysis. Continuing to require research institutions and principal investigators to report research outcomes manually is neither practicable nor desirable. A recent study found that poorly integrated Federal reporting and other regulations impose a heavy and growing administrative burden on Federally funded research [74]. The report argues that this "regulatory overhead" is both large (and getting larger) and inefficient, with many Federal reporting requirements overlapping and even conflicting. It estimates that 42% of faculty time relating to Federally funded research is spent on administrative duties, rather than on the research itself. Not only is an approach using common data sources and consistent methodologies likely to reduce administrative burden, but the cost is likely to be negligible relative to other approaches. Experience with the Longitudinal Employer-Household Dynamics program showed that the cost of processing existing data was about one-half of a cent per record versus over $1,000 per record for survey data collection.

The project called Science and Technology for America's Reinvestment: Measuring the EffecT of Research on Innovation, Competitiveness, and Science (STAR METRICS) is one approach. The core of STAR METRICS is to use digital technologies to capture the data needed to understand and demonstrate the broad scientific, social, economic, and workforce results of Federal science and technology investments, as described in Figure A1. Research institutions are already developing structured information architectures to capture current and more accurate information about the interests, activities, and accomplishments of their scholars [75]. Science and technology agencies in other countries also have developed data platforms to identify and characterize scientific outcomes. An increasing volume and variety of research outputs, such as publications, patents, and datasets, are accessible in digital form and are harvested via services such as Citeseer, Google Scholar, and Microsoft Academic Search. Increasingly accurate methods exist for reliably attributing research products to researchers, a nontrivial task due to considerable ambiguity in author names [76, 77].

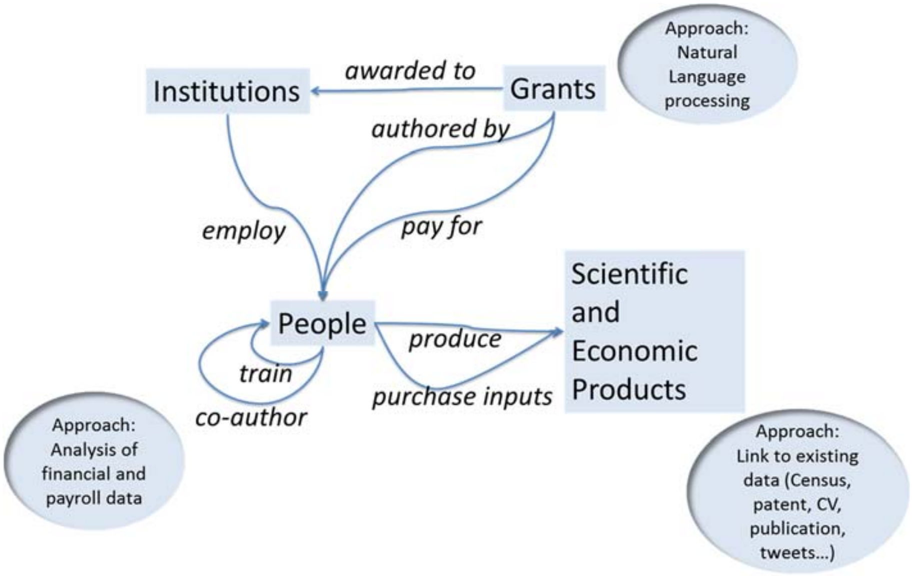


Figure A1. A schematic approach to the analysis of the results of science funding [78].

There are many ways to apply new technologies (Figure A1). The first example is to use tools like natural language processing, rather than manual classification, to describe *what* research is being done using automated analysis of proposal and award text to identify the research topics in a portfolio [79]. The second is to use administrative records to describe *who* is doing research, *with whom*, and with what inputs [39]. Thus, for example, STAR METRICS data from eight Committee on Institutional Cooperation (CIC) institutions have been used to generate a report documenting the research workforce and the short-run economic impacts of Federal research at CIC institutions [39]. The third is to use curricula vitae and other sources of data to describe *what results* the funding has generated [42, 80-82]. One example is the prototype R&D Dashboard (http://rd-dashboard.nitrd.gov/), which was supported by the White House Chief Technology Office and the Chief Information Office.

In practice, this approach means that many measures of scientific and economic activity can be directly generated from existing data, rather than hand curated. For example, in an in-depth and detailed study of the Center for Environmentally Responsible Solvents and Processes at the University of North Carolina, a full time staff person who kept track of statistical information collected much of the data [83]. But many of these direct measures can be automatically generated using a fully-fledged STAR METRICS platform.

Appendix II. Manufacturing Nanomedicine

Fundamental research has advanced nanotechnology in sectors that will require investing in manufacturing infrastructure to successfully commercialize these technologies. Since much of biology carries out at the nanoscale or is mediated by nanoscale structures, the advent of nanotechnology opens up the possibility of bringing a fundamental, engineered approach to medicine. The field of "nanomedicine" has the potential to produce biologically interactive nanoscale materials that prevent, diagnosis, and treat disease; maintain and improve human health; and regenerate tissue. Nano-based approaches have significant advantages over traditional approaches in their potential to modulate biological systems.

A broad array of novel technologies are being developed that have potential to transform the diagnosis and treatment of human disease:

- Nanofabrication technologies can now efficiently generate nanostructures with defined shapes and sizes that can influence particle distribution through the body and uptake by different cell types [84]. This provides a promising technical foundation for developing particle-based approaches for delivering drug payloads to different diseased tissues throughout the body.
- There has been continuous advancement and refinement of nanocarriers that deliver cancer chemotherapeutic agents, including short nucleic-acid oligomers anchored to gold nanoparticles that are taken up quickly and safely into a variety of cell types; multifunctional nanoparticles consisting of self-assembling polymers or micelles that can image and/or deliver synergistic drug combinations; and on-demand release particles that can be autonomously (e.g., pH, temperature) or remotely (e.g., magnetically) controlled to release drug payloads [85-89].
- The biggest advance in diagnostics has been the development of highly sensitive nano-enabled lab-on-chip devices that can detect biomarkers of disease at the femtomol and attomol detection levels and multiplexing portable devices that can give instantaneous readout of biomarkers of disease at the bedside or in the home.
- Nanotechnology is being widely used for antibacterial applications in the hospital environment and is also poised to affect the treatment of infectious disease, e.g., by physically damaging bacterial cell walls and biofilms with mechanisms that bypass antibiotic resistance [90, 91].
- Nanomaterials can have unique capabilities to provide immune modulation, antigen delivery, and immunostimulatory effects [92, 93]. Nanotechnology is also influencing vaccine development for infectious diseases and cancer.

- Novel coatings can be applied to the nanoparticle surfaces to facilitate rapid particle movement across natural, protective mucous barriers. This strategy offers the potential of highly effective delivery approaches to topically treat eye, lung, and gut diseases [94].

Although these examples of nano-based therapies may be fundamentally different in structure and function, they have to overcome common challenges during review and registration by the Food and Drug Administration – the development of defined manufacturing methods that can achieve regulatory approval. A significant emphasis must be placed early in the commercialization pathway on refining or replacing laboratory fabrication procedures with reliable, consistent, and economically viable manufacturing methods that can be scaled up for clinical development and, ultimately, to reliably generate commercial drug supply. Start-ups frequently must focus considerable time and capital on developing these methods. The need to scale up is likely to occur early on the product development timeline since animal testing in the relevant disease models and understanding of how these nanotherapies are distributed in the body are required for making the decision to proceed toward clinical development.

Another important consideration in manufacturing nanomedicines is the need to conduct preclinical toxicity studies and any subsequent clinical trials using drug supply generated under Good Manufacturing Practice (GMP) conditions in an approved facility. Thus this investment must be made prior to knowing whether the nanomedicine will be effective in humans for its intended indication. Depending on the novelty and complexity of the manufacturing process, there may be few options to source the manufacturing to outside parties. In the absence of established nanomanufacturing facilities in which to explore methods, for preclinical studies, complete method validation, or deploy a GMP-based manufacturing scale-up protocol, the start-up has no alternative but do this internally. Clearly, access to manufacturing facilities for scaling up nanomedicines in the amounts necessary for animal testing and preclinical development would accelerate the transition of these novel therapies to proof-of-concept human testing in clinical development.

Appendix III. Review Participants

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