NSTC COMMITTEE ON TECHNOLOGY SUBCOMMITTEE ON NANOSCALE SCIENCE, ENGINEERING, AND TECHNOLOGY

Nanotechnology Signature Initiative

Nanotechnology for Sensors and Sensors for Nanotechnology: Improving and Protecting Health, Safety, and the Environment

Collaborating Agencies:ⁱ CPSC, DOD/DTRA, EPA, FDA, NASA, NIH, NIOSH, NIST, NSF, USDA/NIFA

National Need Addressed

Nanotechnology-enabled sensors (nanosensors) are providing new solutions in physical, chemical, and biological sensing that enable increased detection sensitivity, specificity, and multiplexingⁱⁱ capability in portable devices for a wide variety of health, safety, and environmental assessments [1]. There are many compelling drivers for development of nanosensors. For example, the increasing size and global distribution of agricultural and manufacturing facilities has created an urgent need for sensors that can rapidly and reliably detect and identify the source of pollutants, adulterants, pathogens, and other threat agents at any point in the supply chain. The increasing burden of chronic diseases such as cancer and diabetes in the aging U.S. population requires improved sensors to identify early-stage disease and inform disease management. Several new high-performance nanosensors have already demonstrated rapid response and increased sensitivity at reduced size. However, translation of these devices to the commercial market is impeded by questions about reliability, reproducibility, and robustness.

At the same time, the rise in the use of engineered nanomaterials in commercial products and industrial applications has increased the potential for nanomaterials to be released into the environment, which could pose health and environmental challenges. The impact of nanomaterials on human health and safety and the environment is not well understood, and a greater understanding of basic nanomaterial properties is necessary to detect, identify, and determine potential risk from nanomaterials in the environment. Currently, a very limited suite of devices is available to monitor the release of nanomaterials across the diverse environments where nanomaterials are developed, manufactured, used, and recycled.

The Nanotechnology Signature Initiative, Nanotechnology for Sensors and Sensors for Nanotechnology: Improving and Protecting Health, Safety, and the Environment, addresses both the opportunity of using nanotechnology to advance sensor development and the challenges of developing sensors to keep pace with the increasingly widespread use of engineered nanomaterials. This Nanotechnology Signature Initiative will build upon existing National Nanotechnology Initiative (NNI) member agency efforts to support research on nanomaterial

ⁱ Please note that "collaborating agencies" is meant in the broadest sense and does not necessarily imply that agencies provide additional funds or incur obligation to do so. Agencies are listed in alphabetical order.

ⁱⁱ Multiplexing is the ability of a single device to measure more than one analyte.

properties and development of supporting technologies that enable next-generation sensing of biological, chemical, and nanoscale materials. This interagency effort will furthermore coordinate and stimulate creation of the knowledge, tools, and methods necessary to develop and test nanosensors and to track the fate of engineered nanomaterials in the body, consumer products, the workplace, and the environment.

The NNI's Nanotechnology Signature Initiative on Nanotechnology for Sensors and Sensors for Nanotechnology will accomplish these objectives by means of two major thrusts to:

- 1. Develop and promote adoption of new technologies that employ nanoscale materials and features and the size-dependent properties of engineered nanomaterials to overcome technical barriers associated with conventional sensors, focusing on three goals:
 - 1.1. Support research on nanomaterials and nanoscale device components to enable the next generation of sensors, including tunable, label-free, and enzymatic sensors
 - 1.2. Support development of integrated and portable sensor devices, including information systems support for collection, analysis, and transfer of large amounts of sensor data
 - 1.3. Accelerate commercialization and expand the application base of existing nanosensor technologies
- 2. Develop methods and devices to detect and identify engineered nanomaterials across their life-cycles in order to assess their potential impact on health, safety, and the environment, focusing on three goals:
 - 2.1. Identify and quantify unique magnetic, optical, and electronic signatures of nanomaterials in specific matrices with minimal sample preparation
 - 2.2. Identify "surrogate" indicators of nanomaterial presence
 - 2.3. Design and develop "tags" for nanomaterials that will enable their detection and measurement if released into the environment

The agencies participating in the NNI have recognized the considerable potential for nanotechnology to facilitate the development of inexpensive portable devices for the rapid detection, identification, and quantification of biological and chemical substances. Nanosensors could have significant utility across multiple sectors of the economy, including the healthcare, pharmaceutical, agricultural, food, environmental, consumer products, and defense sectors. Additionally, nanosensors have the potential to empower consumers through their integration into personal data management systems,ⁱⁱⁱ where nanosensors could provide real-time information about personal health metrics, environmental exposures, or energy consumption. Widespread adoption of high-performance nanosensors will require support at each step in the nanosensor development life-cycle, shown in Figure 1. The cycle begins with evaluation of a mission or existing performance requirement and proceeds through research and development, prototype testing, type testing including regulatory approval, production control testing,

iii For example, the Blue Button (bluebuttondata.org) and Green Button (greenbuttondata.org) initiatives.

Nanotechnology Signature Initiative: Nanotechnology for Sensors and Sensors for Nanotechnology 09 July 2012



Figure 1. A life-cycle approach to development and application of sensor sampling methods and instrumentation. Agencies participating in this signature initiative are involved in all stages of this cycle, from funding decisions at the earliest stages, through regulatory review and guidance, post-market surveillance, and sensor deployment. (Adapted from [2].)

training, and acceptance of a method or associated instrumentation to accomplish the mission. Documentation, regulatory guidance, and continuous improvement are essential at each step.

Together the agencies participating in this initiative participate in every life-cycle step outlined in Figure 1, including conducting basic research and development, providing fabrication facilities, developing standards, serving as regulatory authorities, and in many cases serving as the end users for nanosensors. This Nanotechnology Signature Initiative will foster better communication and coordination between agencies regulating or deploying sensors and agencies that support early-stage development efforts. This initiative is intended to enable devices that are better tailored to national needs and may facilitate testing and approval processes.

This initiative will build on successful efforts already underway in the participating agencies. For example, DTRA initiated the program in Ultra-Rapid Next-Generation Pathogen Identification in 2009. The program has developed microfluidic cards for the extraction and amplification of pathogen nucleic acids for use in next-generation sequencing analysis. This technology is scheduled for a field demonstration in 2013 and will identify unknown pathogens in less than one hour, compared to the more than 24 hours needed using existing technology. Also, NIOSH has developed nanosensors to monitor end-of-service life for air-purifying respirators that protect against airborne chemicals [3] as well as miniaturized personal sensors to continuously measure and record, in near real time, particle number, surface area, and mass concentrations of nanoparticle and ultrafine aerosols in the workplace by electrostatics [4] and mobility spectrometry [5].

Technical Program

Thrust 1 of the Nanotechnology for Sensors and Sensors for Nanotechnology: Improving and Protecting Health, Safety, and the Environment Nanotechnology Signature Initiative will exploit the properties of nanomaterials to develop sensors to detect and quantify analytes—including chemical and biological substances and nanomaterials—and support development of the resulting sensors into integrated devices for use in environmental, health, and safety assessments. The goals for this thrust are broken down into three separate areas that are critical to meeting the overarching goal of widespread adoption of high-performance nanosensor technologies across the research, development, and commercialization pipeline. Thrust 2 will foster development of methods and tools to detect, identify, and monitor engineered nanomaterials across their product life-cycles in order to assess the impact of these exposures on the environment and human health.

Thrust 1: Develop and promote adoption of new technologies that employ nanoscale materials and features and the size-dependent properties of engineered nanomaterials to overcome technical barriers associated with conventional sensors.

<u>Goal 1:</u> Support research on nanomaterials and nanoscale device components to enable the next generation of sensors, including tunable, label-free, and enzymatic sensors.

Nanomaterials such as carbon nanotubes (CNTs) and inorganic nanowires offer a very high surface-to-volume ratio and improved electronic properties relative to bulk materials. Acquisition by a nanosensor of a target analyte changes the electronic properties across the entire nanotube or nanowire cross section and produces a large, measurable change, even for a very small number of target analytes, and in some cases, even for single molecules [6, 7]. Theoretical studies estimate that the sensitivity of nanosensors may be three to four orders of magnitude greater than the sensitivity of comparable thin-film-based sensors [7]. The material-dependent physical properties of nanomaterials also make it possible to match the working principle of a detector to the sample matrix (e.g., magnetic detection in optically dense matrices) for improved resolution and performance. In addition, nanoscale detection elements, with sizes comparable to those of the corresponding recognition elements, can provide a high signal-to-noise ratio to provide sufficient total detection.

This first goal of Thrust 1 is to support the development and characterization of detector elements for use in more flexible and higher-capacity sensing platforms. These elements will enable tunable platforms that are sensitive to different analytes and label-free platforms that are compatible with high-throughput devices. Characterization will include identification of new analyte signatures that will signal adulterants in food and pharmaceutical products and clinical samples, as well as environmental pollutants and chemical and biological threat agents. Detection elements capable of fast and direct readout of analytes will also be pursued. In the case of DNA, for example, these technologies have the potential to reduce the time and cost of sequencing and enable sequencing from materials that currently cannot be analyzed, such as highly degraded or fixed samples. Nanosensors can also be designed for improved sample collection and pre-processing and to aid development of portable, rapid-turnaround sensor devices for use in manufacturing and import control, environmental and defense monitoring, and biomedical applications.

The NNI member agencies are already invested in developing new nanosensors, as both funders and early adopters of the technologies being developed. Programs include ONR's Science Addressing Asymmetric Explosive Threats program, which is developing receptor-decorated silicon nanowires and zinc oxide-silicon nanosprings for label-free detection of explosive molecules, and research supported by NIFA on primers and labels for food-borne pathogens and surface-enhanced Raman spectroscopy (SERS) probes for pathogens, toxins, and pesticide residues in food. Participation in this initiative by multiple funding and regulatory agencies will help to ensure that the materials developed are consistent with the needs for real world use and are designed to satisfy applicable regulatory requirements. Expected outcomes for Thrust 1, Goal 1, include:

- 1. Development of tunable sensor platforms capable of multiplexed, multimodal (e.g., magnetic and optical) operation. Ideally, developed nanosensors will be regenerable, allowing repeated use and long-term operation. The platforms should be flexible enough to enable analyte choice at the site of operation.
- 2. Discovery of probes and labels for analytes of interest.
- 3. Label-free sensor schemes for detection of analytes for which no probes are validated or for negative-control-based detection of adulterants in food, pharmaceutical, or medical products, or for detection of environmental pollutants. These sensors should be resistant to fouling and false positives from nonspecific binding events and inherently multiplexed.
- 4. New technologies to directly sequence genetic material, which would eliminate potential bias or errors introduced during DNA amplification. Such technologies would dramatically decrease the genome coverage and bioinformatic reconstruction essential for accuracy with short lengths of DNA, substantially decreasing the cost and burden of data analysis.
- 5. Nanomaterials and nanoscale elements for sample collection and pre-processing.

<u>Goal 2:</u> Support development of integrated and portable sensor devices, including information systems support for collection, analysis, and transfer of large amounts of sensor data.

Optimal design specifications for on-site personal medical diagnostics, environmental and defense monitoring, regulatory inspection, and manufacturing control may often include the smallest possible device size. Portability and sample control also require integration of sample collection, pre-processing, analyte detection, and data analysis in a single device. Material flow between device stages without fouling or loss and determination of how accurately a measured analyte represents the collected sample are important issues that must be addressed before integrated devices can be adopted. Multimodal, multi-analyte nanosensors will produce large volumes of data, so data management strategies are necessary as well. In some cases, the need for small devices makes it preferable that devices perform only essential data processing, and rapid data upload to a data cloud for off-site analysis should be maximized.

Reliable device testing requires standards for collection, organization, and archiving of data. The large amounts of information generated during label and probe discovery and device manufacturing and testing should be archived in databases that are properly annotated with all relevant sample, experimental, and processing parameters included in the metadata. This

annotation is necessary for data to be portable and for results to be comparable across users and applications.

This second goal of Thrust 1 will therefore promote integration of all sensor elements in a single device and to provide informatics support for data analysis. Work supported under this goal will include standards, testing, and infrastructure development, as well as basic nanotechnology research and development. Support for integrated device development is already a priority for participating agencies. For example, several agencies are developing smartphone-interfaced nanosensors, where some of the supported devices are already undergoing field testing. For example, a carbon monoxide nanosensor from NASA's Ames Research Center was tested in September 2011 during a rescue training exercise by the Los Angeles Fire Department. Similarly, results have been published from a clinical trial of a magnetic nanoparticle-based micro-nuclear magnetic resonance device for multiplexed protein detection developed with NIH support at Massachusetts General Hospital [8]. Expected outcomes for Thrust 1, Goal 2, include:

- 1. Test beds for integrated sensors to characterize sample collection and pre-processing and to demonstrate that the measured analyte is representative of the collected sample. These test beds will also provide information on device fouling, cycling, lifetime, and throughput.
- 2. Integrated wireless capabilities in nanosensors to enable off-site analysis and storage of large amounts of data, with implications for improved remote sensing capabilities.
- 3. Infrastructure support for data transfer and analysis from on-site sensor devices, including accessible, open-format databases of nanomaterials, reagents, and labels for use in sensing applications. These databases should include material synthesis and characterization information as well as protocols and standards for the detection of analytes and definition of states (safe or endangered, healthy or diseased).

<u>Goal 3:</u> Accelerate commercialization and expand the application base of existing nanosensor technologies.

Detection and quantification of proteins, oligonucleotides, and organic molecules by several highly sensitive nanotechnology-enabled sensing platforms have been reported over the past decade. Many of these devices integrate microfluidic sample processing designs into the sensors, making the nanosensors highly compact. However, translation of these devices to the marketplace has been slow. Costs have remained high, due in part to difficulties in scaling up production of nanomaterials to industrially relevant quantities while maintaining uniformity, batch-to-batch consistency, and the stability necessary for reliable and robust sensor function. Large-scale manufacturing practices such as advances in integrated circuit manufacturing have not yet been exploited to drive down the price of nanotechnology-enabled device manufacture. Other manufacturing issues related to precise positioning of nanostructures on a large surface include adding probes to the nanomaterial, control of device properties, and yield. Finally, multiplexing capabilities need to be reliably demonstrated.

This final goal of Thrust 1 is to expedite the translation of nanosensor research from the lab to application by addressing scale-up, manufacturing, testing, and regulatory challenges. Effort towards this goal will include standards development and process control and support for

enabling technologies and science, including probe and label testing. These efforts are focused on the later stages of the nanosensor development life-cycle (see Figure 1), and Federal agencies, with their broad reach and varied expertise, are well situated to coordinate these activities. Researchers supported by participating funding agencies are already taking advantage of fabrication support by NIST [9] and regulatory guidance from the FDA. Efforts towards this goal will expand these interactions. Expected outcomes for Thrust 1, Goal 3, include:

- 1. Incorporation of successful nanomanufacturing processes from the data storage, biomedical, and semiconductor industries into nanosensor development. Efforts to achieve this goal will be coordinated with the existing NNI Nanotechnology Signature Initiative on Sustainable Nanomanufacturing.
- 2. Expansion of the application base of existing nanotechnology sensing platforms through the discovery, testing, and regulatory approval of analyte probes and labels.
- 3. Standardization of device performance measurement, including the development of device testing protocols and characterization standards for analyte labels and detector elements. Performance measures may include device linearity and repeatability, temperature stability, moisture resistance, and shelf life for both labels and detector elements.

Thrust 2: Develop methods and devices to detect and identify engineered nanomaterials across their life-cycles in order to assess their potential impact on human health, safety, and the environment.

As the manufacture of engineered nanomaterials and their incorporation into commercial products and industrial processes increases, the potential for nanomaterial release in the workplace and into the environment, and subsequent human exposure, increases. The second thrust of this Nanotechnology Signature Initiative supports development of sensors and tools for the detection and quantification of manufactured nanomaterials in a variety of environmental and biological matrices. Participating agencies have already collaborated on assessments of nanomaterial exposure; one example is the joint project between FDA and the NIH's Nanotechnology Characterization Laboratory at the Frederick National Laboratory for Cancer Research to determine the ability of titanium dioxide nanoparticles such as those found in sunscreens to penetrate skin [10]. The research in this thrust also aligns with several research needs within the 2011 NNI Environmental, Health, and Safety Research Strategy [11]. Collaboration between the participants in this signature initiative and the Nanotechnology Environmental and Health Implications Working Group of the Nanoscale Science, Engineering, and Technology (NSET) Subcommittee will leverage important resources and expedite successful advancement of this thrust.

<u>Goal 1:</u> Identify and quantify unique magnetic, optical, and electronic signatures of nanomaterials in specific matrices with minimal sample preparation.

As the physical and chemical properties of materials change at the nanoscale, it is critical to understand these emergent properties in the context of their physical or biological environments. The first challenge in generating this understanding is the development of sensors and tools to detect and quantify engineered nanomaterials and to distinguish them from incidental and naturally occurring nanomaterials. This is especially challenging for carbon-based nanoscale materials that are naturally occurring, that are produced as a byproduct of combustion and other anthropogenic processes, or that are engineered for specific functions. Given the difficulty in distinguishing between free chemical species and those same species bound in nanoscale materials, detection methods that target the novel and emergent physical properties of nanomaterials (e.g., magnetic or optical) might prove to be most effective.

The expected outcome of Thrust 2, Goal 1, is the identification and description of matrix-specific physical signatures of engineered nanomaterials.

Goal 2: Identify "surrogate" indicators of nanomaterial presence.

Given that it may not be possible to discover unique signatures to directly detect or quantify engineered nanomaterials in some or all matrices, the development of "surrogate" indicators of nanomaterial presence may be necessary. This research will utilize models of nanomaterial migration and transport through synthesis and manufacturing systems and the intended use lifecycle, which will be application-dependent, to identify surrogate materials or markers with properties and behavior similar to those of the nanomaterial of interest. Sensitive monitoring of these surrogates will enable assessment of the containment of nanomaterials during processing and manufacturing. Another class of surrogate indicators for human or environmental health includes metabolites or breakdown species, the detection of which can be used to infer the presence of nanomaterials. Expected outcomes of this goal are:

- 1. Development of models of nanomaterial migration and transport throughout the manufacture and use life-cycle, based on the physical and chemical properties of the nanomaterials. These models will enable identification of surrogate measurements that can be used to infer the presence and amount of nanomaterials in a given environment (e.g., soil, groundwater, or air).
- 2. Testing of assessments of the presence of nanomaterials based on the models developed.
- 3. Discovery of metabolites or breakdown species *in vivo* and in the environment that indicate the presence of engineered nanomaterials or the decomposition of composite materials formed from nanomaterials.

<u>Goal 3:</u> Design and develop "tags" for nanomaterials that will enable their detection and measurement if released into the environment.

Even if surrogate markers or indicators are developed for some engineered nanomaterials, it may still be necessary to develop an alternative strategy to track or quickly identify other engineered nanoparticles. In this case, "tags" that are incorporated into a nanomaterial during synthesis can be used to detect the nanomaterial's presence. These tags can also enable the origins of materials to be quickly determined in order to locate the sources of contamination or exposure. Examples of potential tags include radiotags and other chemical modifications. Tagging nanomaterials to track them from synthesis and manufacture to intended use and subsequent disposal may be the only way to definitively distinguish engineered from incidental and naturally occurring nanomaterials. However, chemical modifications undertaken in order to "tag" a nanomaterial have the potential to change the properties of the nanomaterials, and therefore could potentially affect their environmental fate, safety, and toxicity.

The expected outcome of Thrust 2, Goal 3, is demonstration of tagging strategies and their effectiveness.

Agency Roles and Contributions

Cross-agency coordination in this Nanotechnology Signature Initiative will encourage development of platform technologies that may be modified and used by multiple NNI member agencies to meet their mission-specific responsibilities. At the same time, sensing needs within the different agencies should inform future sensor development to ensure that the utility of each supported platform is maximized. Coordinated efforts in platform development, platform testing, probe discovery, and manufacturing should significantly advance the commercialization and deployment of portable sensors for environmental, health, and safety monitoring. The goals of this initiative are of interest to all participating agencies.

The expertise and perspective that each participating agency will bring to this effort is described below.

CPSC: CPSC staff support the responsible research and development of nanotechnology for implementation in innovative rapid sensing and monitoring devices to improve safety for consumers. The development of novel sensitive, discriminative, and low-cost nanosensors for use in consumer products to detect prehazardous conditions and to provide warning or enable preventive action can reduce likelihood of deaths and injuries. CPSC staff will provide support to the NSET Subcommittee on currently available tools, standards, and approaches to assess the safety, efficacy, quality, and performance of products under CPSC's jurisdiction.

DOD/DTRA: DTRA supports the discovery and development of analytical methods and enabling nanomaterials for rapid and sensitive detection and identification of chemical and biological threats and of new materials to enhance protection against such threats. DTRA also supports the discovery of diagnostic methods for identifying biomarkers indicative of exposure or infection by biological agents, and new approaches in sensor data analysis and algorithms for threat detection.

EPA: The National Center for Environmental Research (NCER) at the EPA has supported research in the development of innovative and rapid sensing and monitoring devices. These devices enable accurate assessment of the environment as well as identification and quantification of environmental contaminants. The research was accomplished through the Science to Achieve Results (STAR) grants program. Additionally, the EPA used the Small Business Innovation Research program as the means by which promising technologies, such as sensors, were solicited and funded.

FDA: FDA supports the responsible development of nanotechnology, including products relevant to nanosensors. FDA will provide guidance on currently available tools, standards, and approaches, as appropriate, to assess the safety, efficacy, quality, and performance of FDA-

regulated products that may incorporate nanomaterials or otherwise involve the application of nanotechnology.

NASA: NASA currently develops nanosensors that are highly sensitive and miniaturized, and that have low power consumption, for detection of chemical and biological species. Applications for these sensors include incorporation into lab-on-a-chip technologies for crew health monitoring, water quality monitoring in the International Space Station, and detection of biomarkers in planetary exploration. NASA also develops nanotechnology-based chemical sensors for a variety of gases and vapors encountered in planetary exploration, Earth monitoring, and aircraft and spacecraft vehicle safety. NASA is also working on the development of nanosensors to measure mechanical strain and detect the early onset of damage in structural materials for use in structural health monitoring for aircraft and spacecraft. The technology and test bed platforms are generic to leverage for biomedical and security applications.

NIH: NIH supports nanosensor R&D programs in biomarker discovery and validation, platform development for multiplexed biomarker detection (including microfluidics platforms, proteomic devices, and SERS instrumentation), multi-analyte arrays for exposure monitoring (both point-of-contact and biomonitoring), molecular probes, DNA sequencing and bioinformatics, and characterization of nanoparticles *in vivo*.

NIOSH: The NIOSH Nanotechnology Research Center (NTRC) has designated *applications of nanotechnology for occupational safety and health* as one of the 10 critical areas in its organized program of research to identify, investigate, and develop science-based solutions to workplace health and safety knowledge gaps in the area of nanotechnology. Through activities such as its Manual of Analytical Methods, NIOSH supports development of guidelines and voluntary consensus standards for identification of sensor needs and objectives; methods development, testing, and certification; user training, documentation, and improvement; sensor acceptance, calibration, and reliability checks; evaluation of operational experience; and periodic performance testing, including realistic applications in complex workplace situations.

NIST: NIST is developing a variety of measurement methods to characterize nanosensors and nanomaterials, and it is creating nanosensors and nanomaterials for measurement applications and standards. Reference materials developed at NIST support the validation of new sensing platforms. The NIST Center for Nanoscale Science and Technology user facility provides access to the tools and processes needed to accelerate the commercialization of nanosensor systems. Research addressing information quality, integrity, and usability will contribute to the reliability and security of sensor networks and data analysis. NIST's complementary nano-EHS programs support the safe manufacture, use, and disposal of engineered nanomaterials and nanotechnology-enabled products.

NSF: Through its Biosensing, Biophotonics, and other programs, NSF supports development of novel sensitive, discriminative, low-cost, and easy-to-operate biosensing systems; innovative ideas in the development of novel biorecognition strategies; multifunctional nanomaterials and interfaces with predefined physical, chemical, or biological characteristics for biosensing applications; and fundamental study of biomacromolecules confinement and orientation at the micro- and nanoscale interfaces for biosensing applications. NSF also supports the development of sensors to detect engineered nanoparticles in a variety of environmental matrices.

USDA/NIFA: NIFA's activities in nanotechnology for biosensors support its mission, strategic goals, and high priorities and apply broadly to plant and animal production systems, food quality and safety, nutrition and health, the environment, and nano-biomaterials. The primary thrusts are in the following areas: (1) Develop novel technologies for characterizing fundamental nanoscale bioprocesses; (2) Construct and characterize self-assembled nanostructures; (3) Develop nanoscale devices and systems incorporating micro-fabrication and nanotechnology; (4) Develop a framework for economic, environmental, and health risk assessment for nanotechnologies applied to food, agriculture, and biological systems; and (5) Produce education and outreach materials on nanofabrication, sensing, systems integration, and application risk assessment.

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