

**AN ASSESSMENT OF THE  
NATIONAL INSTITUTE OF  
STANDARDS AND TECHNOLOGY  
MATERIAL MEASUREMENT LABORATORY**

**FISCAL YEAR 2017**

Panel on Review of the Material Measurement Laboratory at the  
National Institute of Standards and Technology

Committee on NIST Technical Programs

Laboratory Assessments Board

Division on Engineering and Physical Sciences

**A Consensus Study Report of  
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This Consensus Study Report was reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise. The purpose of this independent review is to provide candid and critical comments that will assist the National Academies of Sciences, Engineering, and Medicine in making each published report as sound as possible and to ensure that it meets the institutional standards for quality, objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report:

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Although the reviewers listed above provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations of this report nor did they see the final draft before its release. The review of this report was overseen by Frances S. Ligler, College of Engineering at North Carolina State University and School of Medicine at the University of North Carolina, Chapel Hill. She was responsible for making certain that an independent examination of this report was carried out in accordance with the standards of the National Academies and that all review comments were carefully considered. Responsibility for the final content rests entirely with the authoring panel and the National Academies.



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## Summary

The National Institute of Standards and Technology (NIST)<sup>1</sup> Material Measurement Laboratory (MML) is the nation's reference laboratory for measurements in the chemical, biological, and materials sciences. The staff<sup>2</sup> at the MML engages in fundamental and applied research on the composition, structure, and properties of industrial, biological, and environmental materials and processes. Its research also focuses on the development and dissemination of tools, including reference measurement procedures (RMPs), certified reference (RMs), critically evaluated data, and best practice guides that help to ensure measurement quality.<sup>3</sup>

At the request of the acting director of NIST, in 2017 the National Academies formed the Panel on Review of the Material Measurement Laboratory at the National Institute of Standards and Technology and established the following statement of task for the panel:

The Panel on Review of the Material Measurement Laboratory at the National Institute of Standards and Technology will assess the scientific and technical work performed by the National Institute of Standards and Technology (NIST) Material Measurement Laboratory. The panel will review technical reports and technical program descriptions prepared by NIST staff and will visit the facilities of the NIST laboratory. The visit will include technical presentations by NIST staff, demonstrations of NIST projects, tours of NIST facilities, and discussions with NIST staff. The panel will deliberate findings in a closed session panel meeting and will prepare a report summarizing its assessment findings.

The MML comprises six technical divisions and two offices. The two offices manage programs related to NIST standard reference materials (SRMs) and NIST data products. The technical divisions engage in research and development of the measurement science, standards, technology, and data required to support the nation's need to design, develop, manufacture, and use materials. These divisions interact extensively with both industry and public institutions to advance the economy and provide tools for the creation of knowledge.

The Applied Chemicals and Materials Division (ACMD) examines the thermophysical and mechanical properties of chemicals and materials, analyzes the reliability and performance of materials and structures, and creates information systems for chemical and materials engineering. Such analysis is executed with the intent of fostering innovation and confidence in the nation's physical and energy infrastructures in order to enable advances in chemical manufacturing and electronics, as well as to promote sustainability. The Chemical Sciences Division (CSD) focuses on chemical composition and the chemical structure of gases and organic and inorganic species, and in the measurement of a wide variety of chemical properties and processes—including chemical reactivity and mechanisms and thermochemical properties.

The Biosystems and Biomaterials Division (BBD) quantifies characteristics of complex biological systems, materials, and processes, from the nanoscale to the macroscale, with the intent of fostering

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<sup>1</sup> A full list of acronyms is available in Appendix B.

<sup>2</sup> Please see Appendix A for statistics on the MML's overall staffing by divisions.

<sup>3</sup> The NIST Material Measurement Laboratory, <https://www.nist.gov/mml>, accessed June 30, 2017.

innovation in biomedicine and health care, manufacturing, food safety, environmental health, and national security. The Biomolecular Measurement Division (BMD) develops measurement science and standards for biomolecules such as proteins, nucleic acids, carbohydrates, lipids, and metabolites with applications to biopharmaceuticals, DNA forensics, biomedical and bioscience research, and health care.

The Materials Measurement Science Division (MMSD) develops state-of-the-art instrumentation, analytical methods, models, and software to accurately and precisely measure materials properties, structure, and composition over a wide range of length and time scales for applications such as public safety, forensics, advanced materials characterization, homeland security, and nanotechnology. The Materials Science and Engineering Division (MSED) provides the measurement science, standards, technology, and data required to support the nation's need to design, develop, manufacture, and use materials with the intent of advancing technology and facilitating manufacturing in industrial sectors such as energy, electronics, transportation, and the environment.

The offices serve different functions than the divisions. The MML Laboratory Office houses the MML's executive leadership (director, deputy director, and executive officer); scientific advisor detailees from the divisions; technical program directors; administrative professionals; and specialists for the functions of safety, communications, grants and contracts, information technology, and human subject protections. The Laboratory Office leads strategic planning,<sup>4</sup> solicits and funds exploratory research, coordinates cross-division scientific programs, develops the MML's response to national initiatives, and directs top-level communications with stakeholders and the public. The Office of Reference Materials (ORM) provides business, administrative, product, and technical support for the NIST standard reference materials program. This includes the infrastructure to produce, package, inventory, and market SRM products and then sell them to customers worldwide. The Office of Data and Informatics (ODI), formed in 2014, aims to provide the capacity to handle large and information-rich data sources and transform such data into products, such as NIST standard reference data (SRD), that can be reliably and broadly shared.

Several common themes emerged across the assessments of the MML divisions. MML scientists and engineers interact across disciplinary boundaries and participate in large-scale initiatives that require interdisciplinary collaboration within NIST and across the nation, including increased collaborations with academic, industrial, and other government organizations. The MML is continually refining methods for expanding, coordinating, and improving the efficiency of these interactions. The MML engages in strategic planning; however, communication surrounding strategic plans at the laboratory and division levels could be improved. Further, staff could be engaged more effectively during the strategic planning process. Also, the metrics by which successful performance is judged need to be articulated more clearly.

The general caliber of technical expertise at the MML is competitive with the best large research institutions in the country, but the products generated are generally more varied, because SRD materials and methods are just as important at the MML as seminal publications or patents. The high-quality technical work at the MML—in activities that support the development of standards, SRMs, and SRD, as well as activities focused on performing research—are supported by an excellent equipment infrastructure, which is enabling the MML to meet its technical goals. However, the MML is in high demand by external stakeholders, its relevant technologies are leading edge and dynamically changing, and there is competition for individuals with the expertise required of its staff. The MML therefore faces challenges with respect to achieving an effective balance between maintaining its success in ongoing efforts and initiating new efforts that represent appropriate investment of MML resources in niches that will produce the best impact. These include appropriately allocating the resources of its staff, who are stretched thin in several areas; arranging for staff travel to and participation in activities that maintain and enrich its expertise; maintaining a proper ratio of scientists to supporting technicians; devising succession plans in anticipation of staff who will leave; maintaining an equipment infrastructure by applying

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<sup>4</sup> The Material Measurement Laboratory's Strategic Plan is located at [https://mmlstrategy.nist.gov/sites/default/files/docs/MML\\_Strategic\\_Plan.pdf](https://mmlstrategy.nist.gov/sites/default/files/docs/MML_Strategic_Plan.pdf).

make/buy/borrow/share strategies that provide state-of-the-art capabilities within cost constraints; and ensuring that the mission priorities of MML scientists and NIST's administrative and legal staff are aligned with respect to purchasing of equipment and other resources.

The MML staff participates in many standards organizations and other professional organizations, and the research staff publishes papers in peer-reviewed journals. The MML disseminates its many products broadly and has increasing opportunities to expand its dissemination and outreach activities through improved Internet communications. The following findings and recommendations address key elements in common themes that focus primarily on opportunities to increase the productivity of the MML as a highly valuable and targeted national resource with the potential to play an even greater role in U.S. innovation and competitiveness and to provide an even more broadly based inventory of metrics for use by industry and regulatory agencies.

The MML continues outstanding technical performance in areas related to NIST's traditional endeavors—that is, producing reference materials and supporting the development of international standards. In some cases, the groups in the MML have reached their capacity to support production of reference materials. It is critical for national innovation and industrial competitiveness that leadership in standards development and production of reference materials be supported by first-rate staff and state-of-the-art equipment.

## **CONCLUSIONS AND RECOMMENDATIONS**

### **General Conclusions and Recommendations**

Across the MML divisions, many salient themes were identified regarding the high technical quality of the research, excellence of the scientific staff, strong customer outreach and scientific collaboration, and strong publication and dissemination activities.

While the recommendations below are grouped by divisions to provide actionable suggestions that address each division's unique needs (a focal point of this review), several crosscutting themes, as well as suggestions and recommendations that are thematically similar, were also identified that pointed to opportunities across, or within, the divisions. Specifically, in some of the divisions, such as the ACMD, BMD, and the MMSD, there is an opportunity to take a closer look at balance between long-term goals/research and short-term projects. Such an analysis could help to establish a balanced portfolio of research, as well as maximize the division's manpower and resources. In the case of the inclusion of long-term or high-impact research, it could also help to enable the next generation of measurement tools.

Additionally, some of the NIST staff noted that there was a lack of sufficient technical staff within some of the divisions. This lack of technical support has caused some Ph.D. scientists to do routine tasks like equipment maintenance, which is a poor use of their skills and limits productivity. There was also a concern that postdoctoral fellows have to spend a lot of time learning equipment maintenance and troubleshooting. This can potentially lead to an inefficient use of the postdoctoral fellows, and may also impede their progress toward career goals in research. Also, administrative staff is limited in some areas, and this is causing Ph.D. scientists to do administrative tasks required for their research and development (R&D) work.

It was also noted that the facilities in several divisions, such as the BBD, BMD, CSD, and MSED, are aging and outdated. Some of these facilities have leaking roofs and poor ventilation systems, which makes them inadequate for conducting particular experiments, and limits the range of research that can be performed in those laboratories. Routine requests for maintenance can, in some cases, also take a long time to be addressed.

It was also identified that some divisions, such as the BBD, BMD, and MMSD, could benefit from expanding their working relationships with the Office of Data and Informatics (ODI). Substantial benefits related to data management, leveraging developments made by the divisions, and the establishment of best practices may be realized by pursuing efforts such as these that cross division boundaries.

The review also identified opportunities to better utilize the postdoctoral fellows as well as their network. For example, it was identified that CSD has the opportunity to increase the number and quality of National Institute of Standards and Technology and National Research Council (NRC) postdoctoral fellows within their division. Another opportunity that was identified was through leveraging the postdoctoral fellows' network to improve connectivity across NIST.

Along with suggestions throughout the report, several of the divisional recommendations below reflect these crosscutting or thematically similar topics. Recommendations 1 and 3 both address the theme of finding a balance between long-term goals and research and short-term projects within the ACMD and the BMD—a challenge that was also pointed out in the MMSD chapter. Recommendation 12 focuses on increasing technical and administrative staff in the CSD, which reflects a similar suggestion in body of the report that MMSD also increase technician support. Recommendations 7 and 10 both address facility maintenance in the BMD and the BBD, a topic that was highlighted in the CSD and MSED chapters. Recommendation 6 (which focuses on the BMD) and Recommendation 20 look at expanding the role of the ODI within divisions that have significant data science efforts, a suggestion that is also echoed in the BBD and MMSD chapters. Recommendations 13 and 15 both focus on improving the use of postdoctoral fellows in the CSD and the MMSD. Given that many of these recommendations and suggestions are thematically similar or crosscutting, it may be helpful for MML leadership (divisional leaders, etc.) to meet together to review these suggestions as a whole and to determine where solutions in other divisions may have already been rendered.

### **Applied Chemicals and Materials**

The programs in the ACMD are well thought out and are starting to fit together as the division refines its focus. Some opportunities within the division, such as those in the Fatigue Fracture Group, are associated with finding research efforts that fit with the mature efforts in the group to allow a full spectrum of projects—from mature to high-risk. Further efforts to have a broader range of projects across the high-risk to mature continuum would better position the division to have the available resources and pathways to address critical problems.

**RECOMMENDATION 1: The Material Measurement Laboratory should consider expanding its efforts in such a way that the Applied Chemicals and Materials Division's projects will span the range of development—from high-risk research to mature support programs.**

While the ACMD is doing an excellent job with their dissemination efforts, one way they could facilitate more dissemination is through an exchange program between ACMD personnel and other organizations in industry, universities, and national laboratories. These exchanges could be both to and from the ACMD, with the ultimate goal of expanding dissemination and enhancing the staff.

**RECOMMENDATION 2: The Material Measurement Laboratory should consider an exchange program between the Applied Chemicals and Materials Division personnel and other organizations in industry, universities, and national laboratories.**

### **Biomolecular Measurement**

The BMD excels at addressing the critical measurement needs of the United States in key areas involving biomolecular technologies, including mass spectroscopy, DNA forensics, and biopharmaceuticals. This impact is derived from close interaction with industry and federal agencies. It is important for the division to balance this immediate focus against the upsides of long-term and high-impact research aimed at enabling the next generation of measurement tools, which could lead to



potentially revolutionary advances in future measurement. It was evident that some groups within the BMD were pursuing this type of long-range research (e.g., efforts aimed at the development of methods for single-molecule protein sequencing), and these efforts could be expanded across all groups in the BMD.

**RECOMMENDATION 3: The Material Measurement Laboratory should consider promoting a balanced portfolio of short-term and long-term activities in all groups across the Biomolecular Measurement Division.**

The BMD has identified the compelling need for new measurement standards and methods in the area of precision medicine. It is important to develop a clear set of goals concerning this research in precision medicine and a roadmap for achieving these goals. This roadmap would include the prioritization of target selection for relevancy (e.g., protein biomarkers) and maximizing opportunities for collaboration across NIST (e.g., with the BBD).

**RECOMMENDATION 4: The Material Measurement Laboratory should consider developing a roadmap to realize a program in precision medicine that addresses short-term and long-term needs and maximizes opportunities for collaboration across the National Institute of Standards and Technology.**

The interactions of the BMD with the University of Maryland (UMD) through the Institute for Bioscience and Biotechnology Research (IBBR) have led to synergies between the UMD and NIST. A roadmap is needed to ensure that this productive interaction continues into the future in a manner aligned with the goals of the BMD. This roadmap needs to include the commitment of the UMD to place faculty with aligned research interests in the IBBR. It also needs to describe the role of the IBBR in the context of the strategic goals of the BMD in order to establish new capabilities and expertise to enable protein production, to contribute to the National Institute for Innovation in Manufacturing Biopharmaceuticals (NIIMBL), and to broadly impact biopharmaceutical manufacturing initiatives through improved measurement.

**RECOMMENDATION 5: The Material Measurement Laboratory and the Institute for Bioscience and Biotechnology Research (IBBR) should consider establishing a roadmap that describes the role of the IBBR in the context of the strategic goals of the Biomolecular Measurement Division.**

The multiple divisions of the MML have shared goals (e.g., precision medicine for the BMD and the BBD) and shared capabilities (e.g., genomics in the BMD and the BBD). Groups within the divisions have complementary expertise to address challenges related to data analysis and management. There are, however, relatively few examples of crosscutting interactions that realize these potential synergies between divisions and between the groups of the divisions. The BMD needs to consider creating incentives and mechanisms to stimulate cross-group and cross-division interactions that could create new and existing programmatic synergies between the informatics efforts of the BMD and the ODI, and between the genomic and precision medicine efforts of the BMD and the BBD.

**RECOMMENDATION 6: The Material Measurement Laboratory should consider creating incentives and mechanisms to stimulate cross-group and cross-division interactions between the Biomolecular Measurement Division and the Office of Data and Informatics, and between the genomic and precision medicine efforts of the Biomolecular Measurement Division and the Biosystems and Biomaterials Division.**

The laboratories in which the BMD is located on the main NIST campus are old, and there is a constant need for renovation and maintenance (e.g., to address leaking ceilings). Routine requests for maintenance take a very long time, in some cases months, to be addressed. NIST needs to further improve internal processes for approval and execution of requested maintenance needs in order to protect investments in complex and sensitive instrumentation within the BMD.

**RECOMMENDATION 7: The Material Measurement Laboratory should consult with management of the National Institute of Standards and Technology to consider improving internal processes for approval and execution of requested maintenance needs within the Biomolecular Measurement Division.**

The BMD's website for SRMs is not currently organized around the needs of industry users. It could be reorganized to present SRMs grouped according to industries served by the SRMs (clinical diagnostics, biopharmaceutical, etc.). This has the potential to increase the use of SRMs, increase cost recovery for preparation of SRMs, and communicate to stakeholders the important role that NIST plays in enabling the competitiveness of U.S. industry and commerce. In addition, it will facilitate the adoption of SRMs that are new and not widely known to potential users.

**RECOMMENDATION 8: The Material Measurement Laboratory should consider evaluating the benefits of an improved Biomolecular Measurement Division website that markets standard reference materials for specific industries and federal agencies.**

### **Biosystems and Biomaterials**

The BBD has many ongoing projects and achievements, conducted within and outside of NIST. The BBD staff works closely with other MML divisions. Overall, the division possesses a high level of technical skills and works on cutting-edge science that requires both RMs and standards. The 101 staff members perform work in many areas. The division overall is lean in technical staff but has a superb group of Ph.D. scientists at all levels, from junior to very senior fellows. BBD scientists are conducting outstanding science. Key technical expertise in specialized instrumentation, however, has been lost and not replaced.

**RECOMMENDATION 9: The Material Measurement Laboratory should make a concerted effort to maintain continuity in the staffing of critical positions within the Biosystems and Biomaterials Division.**

Some of NIST's laboratory infrastructure is not adequate for conducting particular experiments crucial to the BBD mission, such as a cell culture up to Biosafety Level 2 (BSL-2) standards. This is owed to dust in older ducts and excess storage in laboratory space.

**RECOMMENDATION 10: The Material Measurement Laboratory should consider engaging with NIST's central operations to find ways to improve the Biosystems and Biomaterials Division's building infrastructure.**

Equipment has an institutional overhead cost of 50 percent to pay for human resources and safety. BBD staff indicated that equipment taxes significantly reduce the amount of equipment they can purchase.

**RECOMMENDATION 11: The Material Measurement Laboratory should consider engaging with NIST’s central operations to find ways to minimize the Biosystems and Biomaterials Division’s overhead burden.**

### **Chemical Sciences**

In total, 115 scientific staff members and approximately 50 associates in the CSD are supported by only 4 technicians and 8 support staff. As a result, Ph.D. scientists are doing most of the laboratory work that could be done by technicians. They are also executing most of the administrative tasks required for their R&D work. To increase the productivity and satisfaction level of its scientific staff, the CSD could provide administrative support for nonscientific tasks and technician support for laboratory work and data analyses that do not require Ph.D. training.

**RECOMMENDATION 12: The Material Measurement Laboratory should consider increasing the Chemical Sciences Division’s support staff both for administrative tasks and for technician support.**

The CSD could maximize the number and quality of NIST and NRC postdoctoral fellows arriving in the division. There are currently no NIST fellows in the CSD and only three of the CSD’s eight groups have an NRC postdoctoral fellow—three in one group, and one in each of the other two groups. The uneven distribution of these fellows among CSD groups and among MML divisions suggests that only a few people are utilizing the best methods for attracting excellent postdoctoral researchers.

**RECOMMENDATION 13: The Material Measurement Laboratory should consider maximizing the number and quality of National Institute of Standards and Technology and National Research Council postdoctoral fellows within the Chemical Sciences Division.**

### **Materials Measurement Science**

The MMSD’s competency database is a good idea; however, the division needs to leverage other databases, such as publications and presentations, from which keywords could be extracted.

**RECOMMENDATION 14: The Material Measurement Laboratory should consider leveraging other databases outside of the Materials Measurement Science Division’s competency database.**

Within the MMSD there needs to be transparency of how to succeed, especially for early career staff. One way to do so is to leverage NIST’s postdoctoral network with a professional development program. Such a program could help to improve connectivity across NIST.

**RECOMMENDATION 15: The Material Measurement Laboratory should consider leveraging the National Institute of Standards and Technology’s postdoctoral network with a professional development program in order to improve connectivity across NIST.**

The MMSD largely excels in the rigor of the data it collects, through applying statistical analysis to optimize the quality of its data and conclusions. One challenge is in the consistency of applying experimental design and statistical analysis across all groups. Uniform application of experimental design (when the project is conducive to it) and statistical analysis is needed. Particularly for exploratory work, the design of experiments would improve efficiency in determining salient variables to explore.

**RECOMMENDATION 16: The Material Measurement Laboratory should consider making the application of the Materials Measurement Science Division’s experimental design and statistical analysis more uniform in order to improve the efficiency in determining salient variables to explore.**

### **Materials Science and Engineering**

The MSED is among the best in the world in terms of computational techniques and researchers. Although the staff is highly knowledgeable, laboratory equipment for making, processing, and to a lesser extent, preparing metallic alloys for testing are basic (with the exception of a new melt spinner for high solidification rate processing of metals). Numerous other facilities worldwide have better metallic processing laboratory equipment.

**RECOMMENDATION 17: The Material Measurement Laboratory should consider updating the Materials Science and Engineering Division’s laboratory equipment used for making, processing, and preparing metallic alloys for testing.**

### **Office of Data and Informatics**

Since its conception, the ODI’s technical activities have been largely focused more on data than on informatics. Now that they have succeeded in improving data access, it is time to work on tools that make the data more useful and easier to analyze. A roadmap is now needed to show management the importance of increasing their resources to enable informatics work and to solicit feedback from their customers on their plans. The MML needs to prepare a 3-year roadmap for the ODI to develop information and analytics tools. A 3-year plan will enable the MML to show how the ODI will ramp up. In years 2 and 3, the ODI can obtain feedback from their customers that will enable them to do longer term planning.

**RECOMMENDATION 18: The Material Measurement Laboratory should prepare a 3-year roadmap for the Office of Data and Informatics to develop information and analytics tools.**

Data preservation is useless unless there is enough associated metadata to enable interpretation of the data years later. The same issue applies to publishing data to satisfy the open data mandate. However, it is tedious to capture and record that metadata manually. To avoid that manual effort and to free up scientists to do science, it would be beneficial if there were an automated system that captures the metadata from instruments and associates it with the data. Therefore, to facilitate data preservation and meet the open data mandate required for government agencies, the ODI needs to acquire or develop a Laboratory Information Management System (LIMS) in order to pull metadata with data from instruments. This would make such data easy to transform into publishable data.

**RECOMMENDATION 19: The Material Measurement Laboratory should consider acquiring or developing a Laboratory Information Management System (LIMS) for the Office of Data and Informatics.**

There has been strong engagement between the ODI, the MSED, and the MMSD through the Materials Genome Initiative (MGI) program. However, there are many other significant data science efforts in divisions within the MML that could be engaged by the ODI. The ODI needs to coordinate and engage with other data science efforts within the MML to learn their best practices in data preservation, curation, and informatics, and to share that learning with all of the MML.

**RECOMMENDATION 20: The Office of Data and Informatics should engage divisions within the Material Measurement Laboratory that have significant data science efforts in order to learn their best practices in data preservation, curation, and informatics, and to share that information with the rest of the Material Measurement Laboratory.**

### **Office of Reference Materials**

The ORM appears to be a highly successful operation that directly supports the mission of NIST and U.S. commerce overall. The ORM operates much differently from the other units within the MML and NIST. It does not conduct the type of research performed by MML divisions, and the majority of the ORM work involves managing and maintaining the SRM sales business that includes marketing, production, sales, quality control, e-commerce, packaging, and distributions. The emerging partnership with the UMD to examine marketing and customer engagement strategies, and similar efforts with other external institutions, is commendable. At the same time, the ORM needs to consider an external examination of its overall business practices, the adequacy of its e-commerce tools, the effectiveness of its marketing and sales operations, as well as other pertinent areas related to its operations.

**RECOMMENDATION 21: The Material Measurement Laboratory should consider an external examination of the Office of Reference Materials' overall business practices, the adequacy of its e-commerce tools, the effectiveness of its marketing and sales operations, and other pertinent areas related to its operations.**

The current allocation of working capital funds (WCFs) and service development funds is increasingly assigned to support recertification and production of existing product lines. This situation may present a risk to the ORM and its ability to produce new materials needed by emerging applications and industrial sectors. The MML needs to develop a strategy to optimize and prioritize the balance between existing product support and the research, production, and certification of new SRMs.

**RECOMMENDATION 22: The Material Measurement Laboratory should develop a strategy for the Office of Reference Materials to optimize and prioritize the balance between existing product support and the research, production, and certification of new SRMs.**

Packaging and distribution is a significant portion of the ORM operations. Appropriate packaging, handling, and long-term storage of SRMs are critical to the ORM mission. Existing capabilities are being stretched to their limit, and in some cases, may not be adequate for anticipated product offerings. NIST needs to undertake an effort to benchmark the state-of-the-art in industrial packaging and storage methods and develop a packaging modernization plan to support the ORM catalog of materials.

**RECOMMENDATION 23: The Material Measurement Laboratory should consider undertaking an effort to benchmark the state of the art in industrial packaging and storage methods and develop a packaging modernization plan to support the Office of Reference Materials catalog of materials.**

As part of a business operations review, the MML needs to examine current staffing and benchmark it against comparable e-commerce operations. Such an analysis would be performed in order to craft a strategic workforce development and staffing plan.

**RECOMMENDATION 24: The Material Measurement Laboratory should examine current staffing in the Office of Reference Materials and benchmark it against comparable e-commerce**

**operations to create a strategic workforce development and staffing plan.**

The MML needs to examine current staffing structures in the ORM that are associated with the recertification of existing products and the development of new SRMs in order to more appropriately assign tasks to research and technician staff, and to encourage SRM-related work as part of the overall measurement science mission of the organization.

**RECOMMENDATION 25: The Material Measurement Laboratory should examine current staffing structures in the Office of Reference Materials that are associated with recertification of existing products and the development of new standard reference materials to more appropriately assign tasks.**

Many of the analytical instruments that are critical to the certification of SRMs within the ORM are dated and do not represent the state of the art. There are commercially available upgrades that may increase the efficiency and effectiveness of the analysis and characterization of SRMs. Many of these measurements and instruments lend themselves to automation, which may reduce the burden on the research staff to perform routine labor-intensive tasks.

**RECOMMENDATION 26: The Material Measurement Laboratory should conceive and implement a plan for replacing, refurbishing, and maintaining analytical laboratory instrumentation housed within the Office of Reference Materials that supports the certification of standard reference materials.**

The space and facilities in the ORM that are needed to store biological materials appears to be reaching a limit in the current warehouse. As the breadth and number of perishable biological items increases, finding appropriate storage facilities and containers may become a significant challenge.

**RECOMMENDATION 27: The Material Measurement Laboratory should develop and implement a plan to accommodate growth in the Office of Reference Materials' storage needs that are associated with perishable biological materials.**

## The Charge to the Panel and the Assessment Process

At the request of the National Institute of Standards and Technology (NIST), the National Academies of Sciences, Engineering, and Medicine has, since 1959, annually assembled panels of experts from academia, industry, medicine, and other scientific and engineering communities to assess the quality and effectiveness of the NIST measurements and standards laboratories, of which there are now seven,<sup>1</sup> as well as the adequacy of the laboratories' resources. The context of this technical assessment is the mission of NIST, which is to promote U.S. innovation and industrial competitiveness by advancing measurement science, standards, and technology in ways that enhance economic security and improve the quality of life. The NIST laboratories conduct research to anticipate future metrology and standard's needs, to enable scientific and technological advances, and to improve and refine existing measurement methods and services.

At the request of the acting director of NIST, in 2017 the National Academies formed the Panel on Review of the Material Measurement Laboratory at the National Institute of Standards and Technology and established the following statement of task for the panel:

The Panel on Review of the Material Measurement Laboratory at the National Institute of Standards and Technology will assess the scientific and technical work performed by the National Institute of Standards and Technology (NIST) Material Measurement Laboratory. The panel will review technical reports and technical program descriptions prepared by NIST staff and will visit the facilities of the NIST laboratory. The visit will include technical presentations by NIST staff, demonstrations of NIST projects, tours of NIST facilities, and discussions with NIST staff. The panel will deliberate findings in a closed session panel meeting and will prepare a report summarizing its assessment findings.

The acting director of NIST also suggested that the panel consider during its assessment the following factors:

1. Assess the organization's technical programs.
  - How does the quality of the research compare to similar world-class research in the technical program areas?
  - Is the quality of the technical programs adequate for the organization to reach its stated technical objectives? How could it be improved?
2. Assess the portfolio of scientific expertise within the organization.
  - Does the organization have world-class scientific expertise in the areas of the organization's mission and program objectives? If not, what areas should be improved?

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<sup>1</sup> The seven NIST laboratories are the Engineering Laboratory, the Physical Measurement Laboratory, the Information Technology Laboratory, the Material Measurement Laboratory, the Communications Technology Laboratory, the Center for Nanoscale Science and Technology, and the NIST Center for Neutron Research.

- How well does the organization’s scientific expertise support the organization’s technical programs and the organization’s ability to achieve its stated objectives?
3. Assess the adequacy of the organization’s facilities, equipment, and human resources.
    - How well do the facilities, equipment, and human resources support the organization’s technical programs and its ability to achieve its stated objectives? How could they be improved?
  4. Assess the effectiveness by which the organization disseminates its program outputs.
    - How well are the organization’s research programs driven by stakeholder needs?
    - How effective are the technology transfer mechanisms used by the organization? Are these mechanisms sufficiently comprehensive?
    - How well is the organization monitoring stakeholder use and impact of program outputs? How could this be improved?

To accomplish the assessment, the National Academies assembled a panel of 23 volunteers whose expertise matched that of the work performed by the Material Measurement Laboratory (MML) staff.<sup>2</sup>

On May 9-11, 2017, the panel assembled at the NIST facilities in Gaithersburg, Maryland, and, concurrently, in Boulder, Colorado, for a two and a half day assessment, during which it received welcoming remarks from the MML director, heard overview presentations by MML management and presentations by researchers at the MML, toured portions of the MML facilities, and attended an interactive session with MML management. The panel also met in a closed session to deliberate on its findings and to define the contents of this assessment report.<sup>3</sup>

The panel’s approach to the assessment relied on the experience, technical knowledge, and expertise of its members. The panel did not attempt to report an exhaustive assessment of every project reviewed. Rather, the panel’s goal was to identify and report accomplishments and opportunities for further improvement with respect to the following: the quality of the technical programs at the MML; the portfolio of scientific expertise within the laboratory; the adequacy of the laboratory’s facilities, equipment, and human resources; and the effectiveness by which the organization disseminates its program outputs. The panel illustrated its conclusions with salient examples of programs and projects that are intended collectively to portray an overall impression of the laboratory, while preserving useful suggestions specific to projects and programs.

To accomplish its mission, the panel reviewed the material provided by the MML prior to and during the review meeting. The choice of projects to be reviewed was made by the MML. The panel applied a largely qualitative approach to the assessment. Given the nonexhaustive nature of the review, the omission in this report of any particular MML project should not be interpreted as a negative reflection on the omitted project.

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<sup>2</sup> See the NIST Material Measurement Laboratory website for information on Material Measurement Laboratory organization and programs, at <https://www.nist.gov/mml>, accessed May 30, 2017.

<sup>3</sup> The agenda for the assessment meeting is presented on the website of the National Academies, at <http://www8.nationalacademies.org/cp/meetingview.aspx?MeetingID=9296&MeetingNo=1>, accessed September 25, 2017.



## Applied Chemicals and Materials

### INTRODUCTION

The National Institute of Standards and Technology (NIST) Boulder campus houses 76 staff members and associates from the Material Measurement Laboratory (MML) Applied Chemicals and Materials Division (ACMD). The division operations occupy multiple locations across the site, with its primary concentration in two buildings.

The personnel at the ACMD characterize the properties and structures of industrially important fluids and materials. Their materials research efforts include the development of fundamental techniques, measurements, and models for analysis of materials structure and reliability. Their fluids research focuses on the characterization of complex mixtures and thermophysical properties. The division was recently reorganized to better align functions with their programmatic plans. Activities of the division are now conducted within the division office and with five research groups.

The division office provides administration and oversight for the division's personnel and resource allocations. The Thermodynamics Research Center compiles and critically evaluates thermophysical and thermochemical data and disseminates this information through a variety of software channels. The Fatigue and Fracture Group provides standard reference materials (SRMs), calibration and measurement services, property data, and predictive models to ensure materials reliability against fatigue and fracture—especially for structural applications (e.g., buildings, bridges, pipelines, and medical devices). The Nanoscale Reliability Group develops and disseminates scientific information, standards, and technology for high-resolution measurements of material structure, chemistry, and physical properties, in order to ensure reliability of materials and devices with critical dimensions in the micrometer to nanometer regime.<sup>1</sup> The Fluid Characterization Group performs experimental research geared toward understanding how the composition of fluids—especially complex fluids—relates to chemical and physical properties, with the goal of property calculation from composition.

The Thermophysical Properties of Fluids Group performs experimental, theoretical, correlative, and molecular simulation research on the thermodynamic and transport properties of fluids and fluid mixtures over wide ranges of temperature, pressure, and composition,<sup>2</sup> including regions of fluid-fluid and fluid-solid phase equilibria.

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<sup>1</sup> NIST, Nanoscale Reliability Group, <https://www.nist.gov/mml/acmd/nanoscale-reliability-group>, accessed September 25, 2017.

<sup>2</sup> NIST, Thermophysical Properties of Fluids Group, <https://www.nist.gov/mml/acmd/thermophysical-properties-fluids-group>, accessed September 25, 2017.

## ASSESSMENT OF TECHNICAL PROGRAMS

### Accomplishments

The ACMD has effectively started the process of refining its focus to align itself to the new (2015) strategic plan and 5-year program plan. That process was undertaken in response to the last National Academies Assessment in 2014. An example of further establishing this alignment is its exit from antibiotic testing by resonance methods, with a good plan for technology transfer to maximize the initial investment in this work. Although that effort was showing signs of success, it was clearly outside the scope of the division.

The following illuminates several examples of outstanding accomplishments in the ACMD groups. The Nanoscale Reliability Group's innovative research is developing techniques to expand the capabilities of scanning electron microscopes through the development of a method for detecting transmitted electrons, which has resulted in unprecedented levels of angular selectivity during transmission imaging. The technology transfer effort, through patents associated with this research activity, seems to be supporting the dissemination of the results to industry. The atom probe effort is a high-risk project that has promise to provide a unique measurement technology for atomic-level chemical identification of a wide range of materials, from liquids (by cryogenic methods) to solids.

The Thermophysical Properties of Fluids Group has strong and rare expertise, which needs to be preserved. Their ability to measure the thermodynamic properties of fluids (gas and liquid) to a very high precision, as well as the coupling of this effort to the equation of state modeling for vapor-liquid equilibrium, is of essential value.

Certain fluid mixtures, such as crude oil and many of the fuels that arise from it, are not readily characterized by the tools used for pure fluids. The ability of the Fluid Characterization Group to describe the properties of such materials, particularly their vapor pressure and solubility characteristics, is essential for fluids validation. The group has also impacted forensic science through the remarkable development of the porous layer open tubular cryoadsorption (PLOT-cryo) method, and its portable version.

The Thermodynamics Research Center Group is dedicated to data and information accumulation and qualification efforts, historically more in the area of fluids, with initial inroads into metals. Their research relates to the Materials Genome Initiative (MGI). A number of methods to input and qualify vast amounts of data are under development.

The Reference Fluid Thermodynamic and Transport Properties Database (REFPROP) standard reference data (SRD) is an essential component of the process simulators utilized globally by industry and has relevance to such areas as climate modeling. The application of the tools to the screening of millions of compounds for low-global warming potential (low-GWP) refrigerants is an excellent example.

The Charpy Impact Machine Verification Program in the Fatigue and Fracture Group provides a very good example of a mature SRM program that is run very effectively. The importance of that effort to industrial quality control of structural materials cannot be overstated and needs to be maintained. The group is making an interesting effort to expand the capabilities of the test. This program is an exceptional example of the close connections that the ACMD has to industry. In addition, the measurement of fracture toughness in high-pressure hydrogen environments to study embrittlement of steels provides a one-of-a-kind capability/facility. The techniques that are being developed allow an order of magnitude more samples to be tested than other approaches.

### Opportunities and Challenges

The opportunities in the ACMD are extensive—for example, the Nanoscale Reliability Group's efforts to design very high speed atomic force microscopy (AFM) capabilities are high risk with equally high potential rewards. The Thermophysical Properties of Fluids Group has some exquisitely accurate and precise measurement techniques. One opportunity might be to dramatically increase the speed of some of

those techniques while minimizing the trade-off in lost precision on their results. Such an effort could lead to the development of new instrumentation useful to industry. The PLOT-cryo effort within the Fluid Characterization Group could yield products in the very near future.

There appear to be groups in various divisions that are related in such a way that they might benefit from being within the same division—one example is the MML research in mechanical properties of solid materials. There are programs in the Materials Measurement Science Division (MMSD) that are also closely related to those in the ACMD. Some parts of the AFM effort in the Fatigue and Fracture Group and an effort concerning nanoindentation could be considered technologies that are related, but at different stages of maturity.

It is not clear what formal programs exist to encourage collaboration between groups in different divisions working on related projects. Each division needs to encourage collaborations between divisions.

The programs in the ACMD are well thought out and are starting to fit together as the division refines its focus. Some opportunities within the division, such as those in the Fatigue Fracture Group, are associated with finding research efforts that fit with the mature efforts in the group to allow a full spectrum of projects—from mature to high-risk. Expanding the efforts to have projects at various stages of development, from high-risk research to mature support programs, would further increase the cohesion in the division. There are diverse interests within the division, and focusing efforts has been a priority since the 2014 National Academies Assessment, with notable progress.

## **PORTFOLIO OF SCIENTIFIC EXPERTISE**

### **Accomplishments**

The scientific staff has many accomplishments of which it can be proud. There are significant accomplishments yielding both external and internal awards. These include the first ever American Gas Association award and a Presidential Early Career Award for Scientists and Engineers (PECASE). Many products of the division are extremely important to a number of stakeholders. The division members are active in standards efforts, as well as publishing a significant number of articles in domain-appropriate peer-reviewed journals, including one article in *Nature Communications*.

Retaining excellent personnel in research areas of high interest at the national and international level (such as in the electron microscopy effort and the AFM effort) can be challenging. While government pay scales are not always competitive, the division seems to have a high retention rate, even in such areas of keen technical interest. This speaks well of the ACMD efforts to promote an attractive combination of work environment and compensation.

The ACMD personnel publish substantially in the open literature, as demonstrated by the links to the Google Scholar sites from the online personnel biographies that are readily available. Publishing is one avenue to monitor stakeholder interest, and the citation rates associated with many of the ACMD personnel are very high. Additionally, ACMD staff members actively participate in seminars, workshops, and conference presentations.

### **Opportunities and Challenges**

One general challenge is the acquisition of specialized personnel to support mature programs in technical areas that are not currently considered high interest at many educational institutions. Simply finding personnel with excellent measurement expertise in any area of research is becoming difficult. Clearly, the division effectively generates new hire opportunities through the National Research Council (NRC) Associateship Program and industrial exchange programs.

The exchange of expertise and examples of collaboration between the two main sites (Gaithersburg, Maryland, and Boulder, Colorado) are somewhat isolated. It appears that the exchange program between

the Gaithersburg site and the Boulder site could be expanded with positive impact on the level of interaction between the sites. A formalization of that effort in an exchange or a sabbatical-type program could be useful. The physical aspects of an exchange process are important as well. Everything from designated office space and on-site housing could have an impact on the success of the exchange program.

The staff in this division is excellent and compares favorably with the staff at other national laboratories. This division is heavily reliant on the retention of personnel from the National Research Council Associateship Program for permanent employees—this cooperation needs to be maintained and encouraged. A concerted effort to nominate staff for external awards could be an effective means to increase the profile of individuals as well as the laboratory itself.

## **ADEQUACY OF FACILITIES, EQUIPMENT, AND HUMAN RESOURCES**

### **Accomplishments**

The combination of facilities available in the ACMD is quite unique. The scientific equipment within the ACMD facilities seems adequate for the mission in most cases, with some pointed exceptions regarding beyond life, critical equipment in the Fluid Characterization Group and the Thermophysical Properties of Fluids Group.

### **Opportunities and Challenges**

There are some improvements in the building facilities since the 2014 National Academies Assessment; however, there are still significant issues. The management seems well aware of these issues and is making progress toward solving the problems; still, continued efforts are needed. Additionally, there are clear frustrations with some of the NIST administrative processes among the ACMD scientific staff. These frustrations were noted in the last report. Specifically, the purchasing process and legal assistance with contracts seems to still be a problem. Additional personnel have been hired to address purchasing process issues, which appears to have resulted in a significant reduction of the problem. Further training of the new administrative personnel associated with the purchasing problem, along with joint meetings between the scientific staff and the new personnel to brainstorm solutions to this issue seems to be in order. There are also some indications of insufficient technician assistance. There may be opportunities associated with further leveraging the uniqueness of the combination of expertise and equipment available in the division. Encouraging groups to extend beyond their comfort zone with regard to maturation of their technology focus may yield positive results. For instance, it may be worthwhile to look for additional new areas of research closely associated with the work being performed by the Fatigue and Fracture Group. In addition, it may be important to look for opportunities to develop standards associated with the Nanoscale Reliability Group's work.

One challenge is the maintenance expenses associated with some of the new equipment. This is an issue at most high-technology laboratories. It is clear that additional help from management with that problem is very important. Some equipment associated with best-in-the-world measurement expertise that has been developed over a significant time frame is clearly at or beyond its expected life.

In general, the facilities and scientific staff are adequate to support the mission of the division. Structural inclusion of maintenance fees in the budget when high-performance equipment is purchased would be helpful.

## **DISSEMINATION OF OUTPUTS**

### **Accomplishments**

As mentioned above, the ACMD personnel publish substantially in the open literature, with 282 archival journal publications, 69 conference proceedings, 24 NIST reports, and 37 books and chapters. This is one avenue to monitor stakeholder interest. ACMD staff members actively participate in seminars, workshops, and conference presentations. The ACMD has worked closely with a variety of agencies, such as with the American Society for Testing and Materials (ASTM), in developing standards. The staff participates in many other standards committees as well—with at least 10 staff members assuming leadership positions on these committees.

There are several favorable examples of programs driven by stakeholder needs that were discussed above—these include the Charpy Impact Machine Verification Program and the Thermophysical Properties of Fluids. A program for which there is significant anticipated stakeholder need is the hydrogen embrittlement testing using the unique high-pressure facilities for fracture toughness testing. The Charpy Impact Machine Verification Program serves over 1000 stakeholders, whose Charpy Testing Machines are being certified by the ACMD, and is an excellent example of monitoring stakeholder use of outputs through SRMs.

The technology transfer office at NIST is available to assist with patent applications and personnel. This suggests that the office has been effective. The ACMD has been awarded 4 patents (and 6 patents pending) over the past 3 years. NIST does not receive financial compensation for patents and stakeholder activity surrounding the patents generated by the ACMD. These patents are monitored by contacts of NIST. NIST chemical property data sets expand capabilities, and in some cases may be an essential enabler of commercial process modeling software available to 45,000 corporate customers and widely taught in chemical engineering academic curricula. Sometimes, a NIST patent is licensed for no fee so that the company associated with technology transfer is protected. One such technology transfer has been pursued to help to efficiently wind down a live bacteria detection program that was outside the identified mission areas of the ACMD.

One novel program, the NIST Science and Technology Entrepreneurship Program (N-STEP) is available and already utilized for entrepreneurial efforts by personnel and serves to transfer NIST activities to the general stakeholder community.

### **Opportunities and Challenges**

Overall, the ACMD does an excellent job of disseminating the outputs of its technical work. One way to possibly facilitate and expand dissemination to more organizations, laboratories, and industries is through establishing an exchange program. Such an exchange program would be between ACMD personnel and other organizations in industry, universities, and national laboratories. These exchanges could be both to and from the ACMD. Making convenient and economic living space available for these exchanges would be valuable, particularly because the cost of housing in the Boulder area is very high. Other organizations, such as universities, have found these kinds of exchange programs very valuable in terms of facilitating and expanding dissemination and the enhancement of staff.

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## **Biomolecular Measurement**

### **INTRODUCTION**

The objective of the Biomolecular Measurement Division (BMD) is to develop measurement technology, standards, and data that can be used to determine the composition, structure, quantity, and function of biomolecules. The work focuses on applied genetics, bioanalytical science, biomolecular structure and function, bioprocess measurements, and mass spectrometry.

The BMD has the following groups and focus areas: the Mass Spectrometry Data Center develops mass spectral libraries for small molecules, metabolites, peptides, glycans, and proteins; the Applied Genetics Group develops standards and technology for deoxyribonucleic acid (DNA) testing to aid human identification and to support biometric, law enforcement, and clinical applications of genetic information; the Bioanalytical Science Group has a research focus in precision medicine and develops protein-based standard reference materials (SRMs) such as urine albumin, C-reactive protein (CRP), and troponin I; the Bioprocess Measurements Group develops methods and SRMs for biophysical characterization of biological particles (protein aggregates and protein-particle surrogate materials as SRMs); and the Biomolecular Structure and Function Group performs crystallography, neutron scattering, and nuclear magnetic resonance (NMR) to determine the structure of biomolecules including protein reference materials and biotherapeutics.

These five BMD research groups carry out their work at the National Institute of Standards and Technology (NIST) Gaithersburg campus and at the Institute for Bioscience and Biotechnology Research (IBBR) in Rockville, Maryland. The five groups have distinct goals but also work on complementary research topics and technical themes directed at the forensics and diagnostics of nucleic acids (DNA), peptides, proteins, and macromolecules—in addition to small molecules. The staff of the BMD that is located at the IBBR carries out work on the characterization of protein and biomolecular structure, which is of relevance to biopharmaceutical measurement and engineering, as part of a collaboration between NIST and the University of Maryland (UMD). The work at the IBBR is enabled, in part, by a 900-megahertz (MHz) NMR spectrometer housed in the W.M. Keck Structural Biology Laboratories. The NMR spectrometer is used for basic and applied research within the BMD related to the characterization of a range of proteins, nucleic acids, and nucleic-acid protein complexes. It is also used to develop models, standards, and databases.

The number of people associated with the research groups of the BMD are given in parentheses: Mass Spectrometry Data Center (32); Bioprocess Measurements Group (22); Biomolecular Structure and Function Group (20); Bioanalytical Science Group (13); Applied Genetics Group (12); and the Biomolecular Measurement Division headquarters (11). A total of 110 people work in the BMD, of which 79 are permanent federal employees (29 female and 50 male). Additional members of the BMD staff include guest researchers and postdoctoral fellows. Thirty-five percent of the division's staff are guest researchers, and 65 percent are federal employees. The overall budget of the BMD in fiscal year (FY) 2016 was \$26.9 million, an increase of 15 percent since FY2014 (\$23.3 million). Sales through the NIST/Environmental Protection Agency (EPA)/National Institutes of Health (NIH) Mass Spectral Library contribute roughly \$6 million to \$7 million annually. There are three primary products of the BMD:

measurement science and protocols disseminated through scientific publications, reference materials and reference data, and mass spectral libraries.

## ASSESSMENT OF TECHNICAL PROGRAMS

### Accomplishments

The overall quality of the technical programs within the BMD is excellent. The BMD has a well-defined mission and focus comprising a portfolio of thrusts that blend established and recognized excellence in mass spectroscopic data libraries and DNA forensics with rapidly growing strengths in biopharmaceuticals and a vision for future impact in precision medicine. The division achieves its impact through an excellent balance between top-down alignment with the strategic goals of the MML and bottom-up freedom given to individual investigators to formulate their own programs consistent with the divisions goals.

The BMD programs have positively impacted U.S. industry by addressing critical measurement needs related to biomolecular technologies. The BMD is achieving much of its success and high impact by working closely with the varied stakeholders to ensure the relevancy of its efforts. This aspect of the division is outstanding.

The Mass Spectrometry Data Center Group is internationally recognized for its technical excellence and sets the gold standard for mass spectroscopy data libraries in the United States. In 2017 this group released and updated a library containing the spectra of more than 300,000 compounds. The group has also expanded its efforts from a historical focus on small molecules to immunoglobulin G (IgG) fragment libraries and peptides, including glycans. The latter focus on reference data sets to enable characterization of glycosylation patterns of proteins is timely and important, as patterns of glycosylation influence the functional properties of monoclonal antibody (mAb)-based pharmaceuticals and are notoriously difficult to characterize. A new initiative to develop libraries for federally controlled substances for forensics, which complements the leadership of the BMD in DNA forensics, is excellent. The large impact of this group is evidenced by the fact that the major U.S. manufacturers of mass spectrometry instrumentation sell the NIST mass spectrometry library installed on their instruments. The Mass Spectrometry Data Center Group is able to recover its costs through sale of the mass spectra reference data sets.

The BMD works with many partners that are involved in regulated industries, including the in vitro diagnostics industry and the biopharmaceuticals industry, as well as federal and academic laboratories. As a neutral third party, the BMD plays two vital roles for these partners: First, because NIST is a nonregulatory agency, the BMD is able to interact with industry, providing objective feedback on precompetitive technologies, without regulatory implications. Second, the BMD enables interlaboratory interactions, as a neutral third party, through the creation of SRMs that can be shared between partners to permit interlaboratory evaluation of measurement methods. These are nationally unique and important roles played by the BMD, and they are exemplified by the Mass Spectrometry Data Center Group in the context of the BMD's development of an SRM mAb (NISTmAb) RM8671. Specifically, the Mass Spectrometry Data Center Group has used the NISTmAb to enable an interlaboratory study of glycosylation analysis involving over 100 laboratories across the world. The study compared the accuracy of mass spectroscopic methods for characterization of glycans. The participating laboratories sent their protocols and results to BMD researchers for analysis and interlaboratory comparisons. The outputs of the study were shared by the BMD with the participating laboratories, which provided the opportunity for the participating laboratories to improve the accuracy of their measurement methods. This type of standardization of measurement methods, which is enabled by the BMD, has the potential to create large sets of self-consistent biological data. This greatly enhances the opportunities to mine the data for information.

The Mass Spectrometry Data Center Group has achieved its impact through the measurement of fragmentation patterns and the dissemination of the results in libraries. The *holy grail* of mass

spectroscopy is the ability to predict how molecules will fragment. This capability is currently not possible, with the exception of peptides. This challenge, if solved, would be a breakthrough in mass spectroscopy. Tackling these sorts of high risk/high reward research veins would be an excellent complement to the more routine, yet important, development of mass spectroscopic libraries currently undertaken by the BMD at NIST. It would contribute to the division's strategic goals of enabling the next generation of measurement tools.

The Applied Genetics Group, whose research focus is in DNA forensics, has developed extensive collaborations with U.S. genomics reagent companies. The group plays a critical role for this U.S. industry by providing objective and neutral assessments of precompetitive technologies. As previously mentioned, the neutrality of the BMD as a nonregulatory agency is a key enabler of this important role. For example, the Applied Genetics Group characterizes, prior to their release, commercial STR profiling technologies for human identification. The Applied Genetics Group also works with, and is funded by, the Federal Bureau of Investigation (FBI), the Department of Homeland Security (DHS), and the Department of Justice (DOJ) to develop and validate methods for human identification. They also have an important impact through the dissemination of SRMs for the forensics genetics community.

The Applied Genetics Group is leveraging its expertise toward DNA-based precision medicine, contributing to the strategic goals of the division related to enabling reliable measurements for precision medicine. The strong connections between this group and industry, in the context of DNA forensics, can serve as a potential model of best practices for the BMD's nascent efforts in precision medicine.

The unified focus of the BMD's Bioprocess Measurements Group and the Bioanalytical Science Group is addressing measurement challenges in biopharmaceutical manufacturing—this focus has blossomed over the past 3 years. These groups have been highly effective in coalescing their efforts around a well-defined set of industry-centric measurement needs, including critical challenges for the U.S. pharmaceutical industry related to protein aggregation and the standardization of characterization methods for mAb production. A key accomplishment of these groups has been the creation of the NISTmAb, which was donated to NIST by Medimmune. As noted above, the existence of this SRM for the pharmaceutical manufacturing industry is enabling interlaboratory studies that are benchmarking analytical methods of characterization of mAbs during production. The outcomes of these studies are being broadly disseminated, as illustrated by the co-editing and co-authoring of a three-volume monograph on the characterization of the NISTmAb, *State-of-the-Art and Emerging Technologies for Therapeutic Monoclonal Antibody Characterization*,<sup>10</sup> which was published by the American Chemical Society (ACS) in 2015-2016. In addition, the BMD is developing reference materials to enable accurate measurement of protein particles in protein-based therapeutics. Overall, the impact of this thrust within the BMD is large and growing rapidly. Key enablers of the success of the BMD in achieving high impact and value are physical proximity to and close interaction with biopharmaceutical companies; proximity to federal agencies such as the Food and Drug Administration (FDA) and NIH; and participation in the National Institute for Innovation in Manufacturing Biopharmaceuticals (NIIMBL). The development of the mAb SRM has the potential to catalyze the development of biosimilars, decreasing the cost and increasing the availability of mAb-based therapeutics in the United States.

### **Opportunities and Challenges**

Overall, the technical programs of the BMD are excellent. As noted above, key personnel and physical infrastructure in the BMD for protein physical characterization is located at the IBBR. The BMD has a clear vision and plan for the role of the IBBR in further development of measurement science and

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<sup>10</sup> J.E. Schiel, D.L. Davis, and O.V. Borisov, *State-of-the-Art and Emerging Technologies for Therapeutic Monoclonal Antibody Characterization*, Volume 1, Monoclonal Antibody Therapeutics: Structure, Function, and Regulatory Space, December 16, 2014, <http://pubs.acs.org/isbn/9780841230262>.



technology for biopharmaceutical manufacturing. Specifically, the BMD strategic plan identifies the opportunity to develop expertise and capabilities at the IBBR to produce mAbs from cell cultures, which are subsequently characterized at the IBBR. The vision is excellent and it integrates the role of NIST and the University of Maryland (UMD) in the NIIMBL. However, it remains unclear to what extent the leadership of the IBBR is committed to this shared vision. It will also be necessary to increase the engagement of UMD faculty with expertise relevant to the bioproduction of mAbs (or other biologics) to achieve the goals of the BMD at the IBBR in the thrust area of biomanufacturing. A roadmap is needed to ensure that this productive interaction between the BMD and UMD through the IBBR continues into the future in a manner aligned with the goals of the BMD. This roadmap needs to include the commitment of the UMD to place faculty with aligned research interests in the IBBR. It would also need to describe the role of the IBBR in the context of the strategic goals of the BMD in order to establish new capabilities and expertise to enable protein production, to contribute to the NIIMBL, and to broadly impact biopharmaceutical manufacturing initiatives through improved measurement.

The rationale for focusing efforts within the BMD on precision medicine is compelling, as the development of robust, reproducible, and accurate *in vitro* assays for protein biomarkers remains an important, yet largely unresolved, challenge. The development of SRMs that can be used to benchmark *in vitro* assays is an important and meritorious goal for the Bioanalytical Science Group within the BMD.

The Bioanalytical Science Group participates with national and international clinical chemistry organizations such as the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) to identify and prioritize development of SRMs for biomarkers, including human serum/urine albumin, CRP, and troponin I. Although these biomarkers have clinical relevancy, the rationale for their choice as initial targets was not well articulated during the review and the Bioanalytical Science Group was not able to provide a prioritized list of future targets. For example, CRP is not recommended by the American Heart Association for the general screening of heart disease. The impact of the Bioanalytical Science Group in precision medicine can likely be increased by engaging more closely with the clinical community and the *in vitro* diagnostics industry. It is important to develop a clear set of goals for research in precision medicine and a roadmap for achieving those goals. Such a roadmap would include the prioritization of target selection for relevancy (e.g., protein biomarkers) and maximizing opportunities for collaboration across NIST (e.g., with the BBD). The Applied Genetics Group and the Mass Spectrometry Data Center Group of the BMD provide good examples of best practices for engaging industry and maximizing relevancy to industrial and federal agencies. Engagement of *in vitro* diagnostic companies making kits for detection of CRP would, for example, ensure relevancy of the efforts of the Bioanalytical Science Group related to the creation of SRMs for CRP.

The Bioanalytical Science Group has been working to develop protein biomarker SRMs in simple buffers and complex matrices, such as patient-derived urine and serum. To date, it issued several protein SRMs in simple buffers, but it has not yet succeeded in developing SRMs based on patient-derived matrices. The accomplishments with simple buffers is good, but the challenge of making reference standards in urine and serum has not yet been overcome despite efforts ongoing since the previous National Academies Assessment in 2014. If the group does not succeed in making progress toward SRMs in complex matrices, an alternative approach would be to use defined, synthetic substitutes for complex matrices. Additionally, obtaining positive patient-derived samples in sufficient quantity for SRMs will be challenging. The use of SRMs based on recombinant proteins may also have merit.

In terms of possible future directions for the Bioanalytical Science Group, two potential opportunities are (1) the development of reference standards for *in vitro* diagnostics of mAbs, as companions to mAbs that are the focus of the BMD groups who are working on biopharmaceuticals, or (2) the development of reference methods and SRMs that permit the evaluation of the functional properties of proteins in *in vitro* assays (e.g., by benchmarking *in vitro* assays against reference methods based on liquid chromatography-mass spectrometry [LC-MS]). In addition, long-range research related to the development of function-structure relationships has the potential to enable future measurement methods for precision medicine.

The BMD also needs to continue investing in long-range research that enables future measurement materials, methods, and data—including high-risk research that could lead to potentially revolutionary

advances in future measurement. It was evident that some groups within the BMD were pursuing this type of long-range research (e.g., efforts aimed at the development of methods for single-molecule protein sequencing).

A broad area of potential long-term impact for the BMD is nano-medicine. Some efforts within the division already fall into this area, including characterization of exosomes, field-flow fractionation, liposome characterization, vaccine characterization, and synthesis of reference nanoparticles based on the cross-linking of amino acids in a flow focusing device.

Last, the BMD excels at addressing the critical measurement needs of the United States in key areas involving biomolecular technologies, including mass spectroscopy, DNA forensics, and biopharmaceuticals. This impact is derived from close interaction with industry and federal agencies. It is important for the division to balance this immediate focus against the upsides of long-term and high-impact research aimed at enabling the next generation of measurement tools.

## **PORTFOLIO OF SCIENTIFIC EXPERTISE**

### **Accomplishments**

The quality of scientific expertise within the BMD is excellent. This excellence is evidenced by the awards they have received over the past three and a half years, including the Gold Medal Award of the Department of Commerce (DOC) and the Mike Lynch Award for the conception and development of the International Chemical Identifier (InChI)—a chemical identifier that was adopted by the International Union of Pure and Applied Chemistry (IUPAC). The DOC has also awarded two Silver Medals—the first to the Applied Genetics Group in 2014 and the other to the Biomolecular Structure and Function Group in 2016. In addition, between June 1, 2014, and February 28, 2017, 16 BMD staff members have been recognized for their work by external organizations, including election as fellows of the American Academy of Forensic Sciences (AAFS) and the IUPAC.

### **Opportunities and Challenges**

The BMD is particularly strong in the structural characterization of proteins. As identified in the strategic plan of the BMD, additional scientific expertise is needed to enable the establishment of protein-production capabilities at the IBBR. Meeting this need will require additional hiring in the BMD or engagement of faculty from the UMD, with expertise in cell culture and protein production. Expertise in cell culture and protein production exists in other divisions of the MML (e.g., the BBD). Interdivision collaboration may be a third element of an approach to address the challenge of establishing expertise in protein production.

Expertise in data management, including analysis and dissemination, is critical to the BMD achieving its impact. Although there is expertise in data informatics within individual groups within the BMD, an opportunity exists to maximize the impact of this expertise and share new data mining approaches (e.g., machine learning-based methods) by creating cross-division sharing of data informatics expertise. Additionally, expertise within the MML Office of Data and Informatics (ODI) can be leveraged by the BMD. As the ODI transitions from being outwardly focused to engaging in internal interactions, substantial benefits related to data management may be realized by pursuing efforts that cross division boundaries. Cross-division interactions also have the potential to benefit the ODI, as best practices established within groups within the BMD can be disseminated across the MML through the ODI.

Overall, as illustrated by the examples presented above related to cell culture expertise and data management expertise, there is an untapped opportunity to achieve impact within the BMD through enhanced intergroup (within the BMD) and interdivision interactions.

## **ADEQUACY OF FACILITIES, EQUIPMENT, AND HUMAN RESOURCES**

### **Accomplishment**

Human resource management within the BMD has been effective in retraining personnel, as the focus of research evolves within the division. For example, a staff member who worked previously on physical measurement standards has received training in biological science and engineering, and is now leading the development of SRMs for characterization of visible protein aggregates in biopharmaceuticals. In general, while requiring alignment with the strategic directions of the BMD, the leadership of the division has provided its scientists with sufficient freedom to define their own focus and contribution to the mission of the BMD. This is a highly effective management style, as evidenced by the high level of staff engagement and the ownership of projects expressed by the staff.

### **Opportunities and Challenges**

The laboratory space occupied by the Bioprocess Measurements and Mass Spectrometry Data Center Groups in the BMD on the NIST campus in Gaithersburg, Maryland, was constructed in the early 1960s. In some of the facilities, evidence of leaking roofs was found. Accordingly, equipment in some laboratories used by the BMD is protected from potential damage from the leaking roofs by the placement of plastic sheets over the equipment. In other laboratory space occupied by the BMD, the ventilation system produces fine particles, which limit the range of research that can be performed in those laboratories. Until the BMD laboratory space is replaced by newer facilities, it can be expected that the laboratory space will require frequent repair and maintenance.

Currently, the time that it takes for repairs and renovation to occur after submission of a request is unacceptably slow. In contrast to the laboratory space occupied by the BMD at this NIST facility, the laboratories at the IBBR are excellent. Given the quality of space at the IBBR, the BMD may wish to explore placement of additional research programs and NIST staff there.

The equipment within the BMD is, in many cases, state-of-the-art for characterization of protein structure. This includes instrumentation for mass spectroscopy and NMR (e.g., the 900 MHz NMR, located at the IBBR). Some of the purchases, like the 900 MHz NMR, were enabled by one-time funding obtained through the 2009 American Recovery and Reinvestment Act.

There is excellent synergy between the Biomolecular Structure and Function Group within the BMD and the neutron scattering facilities of NIST. Both are particularly well suited to address characterization of concentrated protein solutions encountered during the production and formulation of protein-based therapeutics by the biopharmaceutical industry. The proposed purchase of cryogenic transmission electron microscopy facilities for single-protein structural analysis is excellent, and complementary to the neutron scattering and NMR capabilities at NIST.

Discussions with the staff within the BMD revealed a high level of satisfaction with support for acquisition processes, and for the establishment of new contracts of various types, such as the bilateral Cooperative Research and Development Agreements (CRADAs), Materials Transfer Agreements (MTAs), and nondisclosure agreements (NDAs). It was noted that some processes were slow, which reflected the requirements of the federal government, and not the inefficiency of processes within NIST. Overall, the staff expressed satisfaction with its work environment.

In general, the staff articulated a clear understanding of the long-term vision of the BMD. A small number of postdoctoral researchers, however, commented that they did not fully understand how their own professional development is aligned with the overall vision for the future of the division.

## DISSEMINATION OF OUTPUTS

### Accomplishments

The BMD has made a large and tangible impact on U.S. industry and other federal agencies (e.g., the NIH, the FDA, and the FBI) by providing SRMs, RMs, and standard reference data sets. The division has developed and maintains 14 SRMs/RMs and 5 SRDs, including the NIST/EPA/NIH Mass Spectral Library with Search Program, SRD 1A; a humanized IgG1k mAb (RM 8671); a Bovine Serum Albumin (SRM 927e); a Human DNA Quantitation Standard (SRM 2391c); and a Human DNA Quantitation Standard (SRM 2372). The NISTmAb (RM 8671) can be highlighted as an example of the impact of an SRM developed by the BMD. The NISTmAb (RM 8671) was shared and characterized from 2013 to 2015 by more than 100 participants from 11 biopharmaceutical companies, 5 instrument vendors, 5 universities, and the FDA.<sup>11</sup> As previously mentioned, the characterization data formed the basis of a three-volume ACS book series, *State-of-the-Art and Emerging Technologies for Therapeutic Monoclonal Antibody Characterization*, published in 2015-2016.

Over 30 different analytical methods were used under industry best practices to characterize the NISTmAb (RM 8671). This partnership was highly successful and serves as a model for future SRM products. The NISTmAb (RM 8671) was issued on July 28, 2016, and as of April 4, 2017, over 350 units were purchased. The customers include nearly all top-20 global biopharmaceutical companies (30 percent), major analytical instrument companies (30 percent), and private contract research and manufacturing organizations that support biopharma (15 percent).

In addition to being assigned a concentration value traceable to ultraviolet–visible spectroscopy (UV-Vis) transmittance, assays were developed per International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use guidelines for size, charge, identity, and stability that are included in the certificate for NISTmAb (RM 8671). The BMD has also disseminated important advances in measurement methods, through high-impact publications and presentations at conferences. Between June 1, 2014, and February 28, 2017, staff members in the BMD published 14 books and book chapters, 157 archival journals, 22 conference proceedings, and 13 NIST reports. As an example of the high impact of BMD publications, the BMD was the first to demonstrate that the structure of mAbs could be mapped by two-dimensional (2D) NMR techniques at natural abundance. The accomplishment was published in the journal *Analytical Chemistry* in 2015.<sup>12</sup> Since the fall of 2014, the Applied Genetics Group has generated 39 publications and 86 oral presentations.

The BMD achieves its high impact through close interactions with industry, which is evidenced by the large number of MTAs and CRADAs in which the BMD has participated. Between June 1, 2014, and February 28, 2017, the BMD executed a total of 177 total agreements (including 141 MTAs and 4 CRADAs) with industry partners.

### Opportunities and Challenges

Overall, the dissemination of outputs within the BMD are excellent. Four additional observations are offered. First, as noted above, the BMD reference standards have had an important impact on the measurement capabilities of the United States. This high impact has occurred with minimal marketing by NIST. In particular, the website for SRMs is not organized around the needs of industry users. The website could be reorganized to present SRMs grouped according to the industries served by the RMs

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<sup>11</sup> NIST, “Made to Measure Building the Foundation for Tomorrow’s Innovation in the Biological, Chemical, and Materials Sciences,” p. 116, 2017.

<sup>12</sup> L.W. Arbogast, R.G. Brinson, J.P. Marino, Mapping monoclonal antibody structure by 2D C-13 NMR at natural abundance, *Analytical Chemistry* 87(7):3556-3561, 2015.

(clinical diagnostics, biopharmaceutical, etc.). This focus on marketing has the potential to increase the use of NIST SRMs, increase cost recovery for the preparation of SRMs, and communicate to stakeholders the important role that NIST is playing in enabling the competitiveness of U.S. industry and commerce. In addition, it will facilitate the adoption of SRMs that are new and not widely known to potential users. The potential exists for even greater impact through the optimized marketing of SRMs, in particular, to industry and federal agency stakeholders. An increase in the use of SRMs prepared by NIST, however, will also necessarily require additional investment of resources within NIST to ensure a reliable supply of SRMs (particularly, when they are integrated into regulated manufacturing processes) and the capacity to address customer problems and needs when they arise. Second, as SRMs produced by NIST are increasingly integrated into U.S. manufacturing processes, it will be important for NIST to provide sufficient infrastructure support to ensure that the supply of the standards is reliable. The absence of the timely provision of SRMs used in critical pharmaceutical manufacturing processes has the potential to halt production of important medicines.

Third, a key output and impact of the Applied Genetics Group, whose research focus is in DNA forensics, revolves around the evaluation of new technologies for forensic analysis. Developers of new reagents and instrumentation send their technologies to NIST for independent and objective third-party evaluations. This service plays a critical role in establishing the high quality of forensic technologies in the United States; however, it also occurs through an informal process that involves collaboration. This informality potentially limits access to this valuable resource, as it may be unknown to new companies developing DNA forensic technologies. Last, the dissemination of the mass spectroscopic libraries by the BMD has an important impact on measurement by mass spectroscopy worldwide. Substantial income in the form of cost recovery is derived from the sales of these libraries, but the pricing of the libraries is largely historical and not based on a pricing or cost study. Additional cost recovery has the potential to provide additional resources that will enable further development of the libraries.

## Biosystems and Biomaterials

### INTRODUCTION

The overarching goal of the Biosystems and Biomaterials Division (BBD)<sup>1</sup> is to develop and disseminate standards and measurement technology to support quantitative biological and biomaterial measurements. The BBD consists of four technical groups: the Microbial Metrology Group, the Bioassay Methods Group, the Biomaterials Group, and the Cell Systems Science Group. Additionally, the Joint Initiative for Metrology in Biology (JIMB) program, in partnership with Stanford University, reports directly to the MML.

The BBD leverages cross-functional teams of material scientists, molecular biologists, engineers, chemists, physicists, statisticians, and data scientists who are some of the world's best technical experts. These experts carry out fundamental research in biological measurement science and the development of reference methods, advanced analytical instruments, reference data, and methods. The BBD has 101 staff members—90 percent are scientists and associates, and the remainder are technicians and support staff.

The activities of the BBD are focused on existing and anticipated applications of biological and biochemical science in products and processes that influence manufacturing, natural resources, and health care. The BBD approach is to develop technical excellence in core measurements that serve a number of applications, including regenerative medicine and advanced therapies, cancer diagnostics, the engineering of biological systems, nanoparticle safety, dental and oral health, and microbial identification and quantification. To achieve its mission, the BBD employs technical expertise in genomics measurement assurance; the quantitative measurements of cells; the development and deployment of imaging and spectroscopy technologies, including broadband coherent anti-Stokes Raman scattering (BCARS) microscopy and live-cell imaging; and in the development of biomaterials—particularly for dental applications.

### ASSESSMENT OF TECHNICAL PROGRAMS

#### Accomplishments

The Microbial Metrology Group develops advanced measurements and standards for the exploitation of microbes to promote human health, precision medicine, advanced manufacturing, and other industrial applications. The group uses genomic and metagenomic approaches to improve measurements on

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<sup>1</sup> Some of the background information within this chapter was derived from the document NIST, “Made to Measure—Building the Foundation for Tomorrow’s Innovation in the Niological, Chemical, and Materials Sciences,” pp. 94-111. 2017.

microbiomes, and is also developing RMs for assessing the sensitivity and specificity of pathogen detection devices.<sup>2</sup> Additionally, the group utilizes advanced methods, including microfluidics, predictive modeling of engineered microbes, bioinformatics, and state-of-the-art imaging, which are being applied to critical areas, such as combating antibiotic resistance, food safety, clinical diagnostics, and engineering biology.<sup>3</sup>

The Microbial Metrology Group's accomplishments include microbial community measurements, pathogen detection and identification, biothreat detection, and microfluidic development.

The Bioassay Methods Group develops standards and methods for improving confidence in fundamental measurements in biology through new and improved techniques, methodologies, and standards based on optical and genomic methods. The group is focused on improving the quantitative measurements of the biological markers of gene expression in eukaryotic cells and biological fluids. It is providing tools that can be used for bioanalytical measurements pertinent to instrument calibration and analytical validation.<sup>4</sup> It is also working with stakeholders in the research and clinical analysis communities to determine their needs and opportunities, so that they can determine where to strategically focus their efforts. It has identified existing and future standards needs, ranging from device calibration and instrument performance to the development of biological RMs and procedures.

The group has active projects in the development of genomic standards to support: cancer diagnostics and therapeutics, RMs for quantitative flow cytometry, development of genomic markers for cell line authentication, and measurements for assessing the results of genome editing.<sup>5</sup> Their accomplishments include the production of standard reference material (SRM) 2373, a human epidermal growth factor receptor 2 (HER2) genomic DNA standard for gene copy number produced from five breast cancer cell lines. This SRM is discussed in greater detail below.

An ongoing project of the group is the analytical validation and quantitation of circulating tumor DNA (ctDNA) through liquid biopsy. This project is being developed in partnership with SeraCare, an industry partner, and in collaboration with Early Detection Research Network (EDRN)-funded laboratories.

Projects in the planning phase include expanding a suite of RMs to include epigenetic markers, as well as liquid biopsy measurements of gene copy numbers, translocations, and other biomarkers. Other biomarker projects include quantitative flow cytometry assays for chronic lymphocytic leukemia (CLL) and myeloma markers for residual disease during therapy. Another project is to develop SRMs for cell-free DNA noninvasive prenatal screening.

The Biomaterials Group develops advanced measurement capabilities and measurement assurance strategies for characterizing biomaterials, biological systems, and their interactions. The Biomaterials Group aims to provide quantitative measurements and the prediction of chemical, physical, structural, and mechanical properties on multiple length and time scales. One major focus is the development of nonlinear optical spectroscopy and imaging methods for extracting statistically significant information from biological and material systems.<sup>6</sup>

The Biomaterials Group has also developed and delivered a yeast surrogate biothreat test material, which is engineered yeast material containing a target DNA sequence as a surrogate for pathogenic agents that enables safe on-site training for first responders to increase confidence in biothreat detection. It has been used in field deployment exercises in conjunction with the Department of Homeland Security (DHS) and the Army. The group is also addressing antibiotic resistance—a global health crisis—by developing

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<sup>2</sup> NIST, Microbial Metrology Group, <https://www.nist.gov/mml/bbd/microbial-metrology>, accessed September 25, 2017.

<sup>3</sup> Ibid.

<sup>4</sup> NIST, Bioassay Methods Group, <https://www.nist.gov/mml/bbd/bioassay-methods>, accessed September 25, 2017.

<sup>5</sup> Ibid.

<sup>6</sup> NIST, Biomaterials Group, <https://www.nist.gov/mml/bbd/biomaterials>, accessed September 25, 2017.

microfluidic *microenvironment* devices that establish antibiotic concentration gradients to challenge bacteria and measure the evolutionary process.

Additionally, the Biomaterials Group develops measurement assurance strategies to obtain high-confidence results when measuring cells (mammalian and bacterial), materials, and their interactions. Collectively, these efforts are expected to facilitate the development and translation of new diagnostics and advanced therapeutics (protein- and cell-based), enable better biothreat detection, and improve the performance of biomaterials.<sup>7</sup>

Recent developments within the Biomaterials Group include the rapid broadband coherent anti-Stokes Raman scattering (BCARS) microscopy of cells, tissues, and materials; novel spectroscopy for probing higher order molecular structures and orientation; and new methods for probing fast molecular dynamics. The projects integrate experimental and computational approaches to understand multiple material properties during polymerization in order to enable better materials design through chemical and processing controls. Additionally, the methods used by the Biomaterials Group have been applied to the quantitative imaging of stem cell populations and chemical imaging of cells and tissues with Raman spectroscopy—offering an innovative proteomics resource.

The Cell Systems Science Group contributes to the new postgenomic era with research in measurements and models that support the understanding of complex biological phenomena at the cellular and subcellular levels. The group focuses on the cell as a system and on tools that can make measurements and characterize the system's properties.<sup>8</sup> This is achieved through bioimaging and other cytometry techniques, measurements that assess protein and gene function within living cells, experimental design, and bioinformatics.

The group is focusing on measurements for assessing the process of creation, maintenance, and differentiation of pluripotent stem cells, in addition to cell lines and engineered cells, to better understand cellular dynamics. They are also emphasizing new measurement tool developments and protocols that ensure reliability and comparability of cell assay and imaging-based measurements, as well as appropriate data analysis and data handling pipelines. These efforts assist basic biomedical research, biomanufacturing of regenerative medicine products, nonanimal toxicology testing, drug development and testing, precision medicine, and other applications that depend on understanding and predicting complex cellular activities.<sup>9</sup> Recent projects include detecting and measuring single-molecule RNA-fluorescence in situ hybridization (RNA-FISH) in bacteria, new approaches for cell counting and RMs, and new methods for flow cytometry.

The JIMB is a joint venture between NIST and Stanford University in Palo Alto, California. The JIMB was conceived to connect NIST science, technology, and metrology to the creative power of Stanford University's research, faculty groups, and medical school—embedded in the innovation hub of Silicon Valley. The JIMB is powered by the partnership of NIST with Stanford and Bay area commerce in bioscience and biomedical instrumentation. The JIMB's current focus is on reading and writing DNA, a conscious nod to its Silicon Valley home and its legacy. JIMB arrives at Stanford at a time when Silicon Valley is poised for growth in biology.

The JIMB's accomplishments include the development of methods and tools for genomics and bioinformatics analyses and continuous collaboration with many stakeholders, such as public-private-academic consortia. The JIMB hosts three consortia: the External RNA Controls Consortium (ERCC); the Genome in a Bottle Consortium (GIAB), and the Synthetic Biology Standards Consortium (SBSC). In total, there are more than 150 different partners in these consortia with varying degrees of engagement, working together to develop standards for RNA measurement, for genomic DNA measurement, and for various elements in the emerging synthetic biology community.

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<sup>7</sup> Ibid.

<sup>8</sup> NIST, Cell Systems Science Group, <https://www.nist.gov/material-measurement-laboratory/biosystems-and-biomaterials-division/cell-systems-science-group>, accessed September 25, 2017.

<sup>9</sup> Ibid.



ERCC measurement science products include the NIST SRM 2374 DNA Sequence Library for External RNA Controls, and the turn-key analysis software, *erccdashboard*, which evaluates the technical performance of any gene expression experiment. The ERCC is creating new standards and measurement science to support new and emerging quantitative evaluation of transcriptome measurements, ERCC 2.0.

In May 2015 NIST released an RM of a pilot GIAB sample, which has been widely used for technology development, optimization, and demonstration, as well as by clinical and research laboratories to assess performance. Specifically, this project produced the genome in a bottle RMs and includes RM 8398 (a European ancestry genome), which was released in the spring of 2015; three new human genome RMs; and one microbial genome RM, which was released in the fall of 2016. These RMs are supporting the precision medicine initiative.

The JIMB has held several public workshops highlighting the need to understand the quality of results from next-generation sequencing (NGS). At the September 2016 workshop, NIST announced the release of four additional extensively characterized human genomes as NIST RMs, and these cell lines are already included in several commercial products to meet additional reference sample needs.

The JIMB has refined the SBSC strategy to focus on developing standards products that would improve the accuracy and efficiency of transactions in the synthetic biology workflow. Example transactions include nucleic acid sequence information standards to support the accurate use of nucleic acid materials, or technical standards to support the accurate transfer of an organism from a research and development (R&D) bench to an industrial-scale fermenter.

The BBD's regenerative medicine-related activities include cell counting, live cell imaging, flow cytometry, genome editing, tissue engineering (TE), standards leadership, and customer outreach. Cell counting and viability are key measurements that are critical for decision making—from R&D to manufacturing—but are known to have large measurement variabilities. The BBD recently developed an approach for evaluating the quality of cell counting measurements through experimental design and statistical analysis. The NIST approach represents a paradigm shift from traditional approaches that rely largely on highly specific RMs. In addition, the experimental design and statistical method is agnostic of the cell type and counting method, making it broadly applicable to many counting applications. A user interface is under development to allow broader adoption of this method as an international standard and a research tool.

Live-cell imaging tools allow the BBD to monitor spatial information and population heterogeneity on large numbers of individual cells. High-quality data obtained using benchmark materials may be used to develop predictive models based on stochastic fluctuations and may also provide reference data. Such data may have the potential to be used to validate putative molecular markers for pluripotency and differentiation, and for evaluating markers of product potency. The BBD is also developing advanced measurement capabilities, including quantitative label-free imaging, such as BCARS imaging, for characterizing cell state and cell-biomaterial interactions.

Flow cytometry, while widely used in characterization of cell populations, is notoriously variable from instrument to instrument and location to location. The BBD works with stakeholders to make flow cytometry a quantitative tool that can provide comparable data across laboratories by developing benchmarking materials and protocols—including fluorescence standards for calibrating beads and lyophilized cell RMs.

Genome editing products and processes need reliable methods to ensure sound results of the editing and to add confidence to the safety of the operation, and the likely effectiveness. The BBD is working with stakeholders, including through NIST-organized workshops, to identify precompetitive technology, measurement, and standardization needs and solutions. The current program focuses on evaluating assays and informatics tools and on the development of RMs. It is also in the process of establishing a NIST-led consortium to develop measurement solutions and standards to advance this technology space—specifically, quantitative flow cytometry.

Current efforts of the BBD also include the development, quantification, and modeling of polymeric and inorganic TE scaffolds, as well as quantifying cell-materials interaction. Through the study of many cell types for regenerative purposes, it has developed various methods to produce TE constructs,

including electrospinning.

Standards are critically needed to assist in the development and regulation of advanced therapies. The BBD is working to develop documentary standards with key stakeholder input from the American Society for Testing Materials International (ASTMi) and the International Organization for Standardization (ISO). The BBD also coordinates broader industry discussion through administering and chairing the U.S. Mirror Committee to ISO/TC276: Biotechnology, and they also serve as convener of the Working Group on Analytical Methods within ISO/TC276.

The BBD also has collaborations with industry (Lonza, Pluristem, Nexcelom, etc.), federal agencies (the National Institutes of Health [NIH] and the Food and Drug Administration [FDA]), and international metrology institutes (in the United Kingdom, Japan, etc.) on precompetitive measurements. Additionally, they have joint research projects with the FDA to address cell measurement challenges and flow cytometry.

The BBD's capabilities in metagenomics include microbial community measurements utilizing metagenomics approaches in the microbial community (microbiomes and biofilms). The BBD is also developing prototype RMs, reference data, and reference protocols to identify, understand, and eliminate measurement bias. Additionally, it is developing pathogen detection and identification utilizing metagenomic techniques, which are emerging as superior methods, as they alleviate the need for targeted approaches that are subject to bias in their design. In collaboration with the FDA Center for Devices, the BBD is also developing a mixed pathogen DNA RM that can be utilized to assess the analytical sensitivity and specificity of NGS-based pathogen detection devices in the clinical setting. Metagenomic methods for pathogen detection are also being adopted in the biomanufacturing industry, where determining the presence of a bioburden (microbial or viral contamination) is necessary for current Good Manufacturing Practices (cGMP) biomanufacturing. RMs for biothreat detection are also being developed under an interagency agreement with the DHS. As mentioned, a yeast-based material tagged with a specific genomic sequence served as a surrogate agent in a field test, and continues to be studied for further qualification.

Custom-engineered microfluidic microenvironment devices that can establish chemical (antibiotic) concentration gradients are being used to challenge bacteria and measure the evolutionary process. The emergence and spread of antibiotic resistance is a global health crisis, and the BBD is developing novel measurement tools that will allow it to measure and better understand the process by which bacteria evolve resistance to existing and novel antibiotics. These new measurements can ultimately provide a new metric, known as the *resistance potential*, that describes the probability that a strain of bacteria can evolve resistance to an antibiotic. Ultimately, this new resistance potential metric can be used to develop novel antibiotics that are more resistant to resistance. Further, these new measurements could be used by health care providers to make better informed clinical decisions.

In reference to the BBD's customer outreach, the International Metagenomics and Microbiome Standards Alliance (IMMSA) is a nonhierarchical association of microbiome-focused researchers from industry, academia, and government that is hosted by NIST. The IMMSA brings together a broad and diverse community of stakeholders who all have a vested interest in improving confidence in microbiome measurements. IMMSA was formed for the mutual benefit of the entire microbiome and metagenomics community and focuses specifically on coordinating crosscutting efforts that address microbiome and metagenomic measurement challenges. IMMSA members are representative experts for all major microbiological ecosystems (e.g., human, animal, built, and environment). These experts are from various scientific disciplines, including, but not limited to: microbiology, 'omics, epidemiology, bioinformatics, and statistics.<sup>10</sup>

In terms of the BBD's achievements and impact on the scientific community, the BBD was represented on the Fast-Track Action Committee on Mapping the Microbiome, which was organized and

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<sup>10</sup> NIST, Biosystems and Biomaterials Division, "IMMSA Mission Statement," updated January 5, 2017, <https://www.nist.gov/mml/bbd/immsa-mission-statement>.

hosted by the White House's Office of Science and Technology Policy (OSTP). This committee published a report that was an assessment of microbiome research in the United States and identified gaps or needs for translating basic research to commercial applications for health care and agriculture. This committee found, nearly unanimously, that there is a need for standards and RMs to increase interlaboratory comparability and confidence in microbiome measurements.

The BBD develops RMs for cancer biomarkers that improve measurements in basic and clinical research. The RMs are developed in consultation with cancer experts from industrial, academic, and government laboratories. As mentioned, the BBD developed a NIST SRM for the HER2, gene, which is frequently amplified in breast cancer. The standard consists of purified genomic DNA from five breast cancer cell lines with different amounts of HER2 gene amplification. This RM is available from NIST as SRM 2373.<sup>11</sup>

The BBD is also currently preparing an RM for measuring the receptor tyrosine kinase for proto-oncogene MET and epidermal growth factor receptor (EGFR) genes. This new standard, when completed, will be available as RM 8366. The standard consists of purified genomic DNA from six different cancer cell lines. The program will enable new diagnostics and therapeutics for cancer to be made by developing robust and reliable tools for measurement assurance, which includes RMs, protocols, and analysis pipelines.

The BBD supports the National Cancer Institute's (NCI's) EDRN as a Biomarker Reference Laboratory by efficiently validating the measurement of specific cancer biomarkers as identified by the EDRN discovery laboratories. It also identifies critical areas where improvements in the measurement infrastructure will significantly impact the quality of the biomarker measurements. An interlaboratory testing program using candidate RMs for ctDNA is in progress to improve the accuracy and reliability of the measurements of new biomarkers for early cancer detection.

The BBD has a long-standing relationship with the NIH/NCI/EDRN, where NIST acts in a network of Biomarker Reference Laboratories. The BBD works with this network of partners by piloting interlaboratory studies in microRNA (miRNA) measurements and measurements of genomic mutations (including in ctDNA), and in evaluating a mitochondrial deletion biomarker of prostate cancer.

The BBD collaboration with SeraCare Life Sciences to advance the development of ctDNA diagnostic assay RMs is ongoing. Under the agreement, NIST will manage an interlaboratory testing program of the EDRN cancer biomarker discovery using RMs developed by SeraCare. NIST is also working with the Foundation for the NIH to plan a much larger testing program of clinical laboratories and commercial testing laboratories using RMs developed by multiple suppliers. The testing program will begin with analytical validation of the methods used in the clinical and commercial laboratories and will be extended to include clinical validation of cancer biomarkers used to determine treatment.

An informal collaboration is ongoing with the Molecular Characterization Laboratory (MCL) at the Frederick National Laboratory for Cancer Research. The MCL is one of four laboratories that does the measurements for the precision medicine NCI, Molecular Analysis for Therapy Choice (NCI-MATCH) clinical trial. The BBD is collaborating in the application of NIST cancer biomarker standards and in developing new standards based on cancer diagnostic and therapeutic needs in order to improve the accuracy and reliability of their measurements. As mentioned, they are also in the process of developing the NIST RM 8366, and have three publications in peer-reviewed journals.

An interlaboratory assessment of ctDNA samples in the EDRN discovery laboratories is also in progress. The initial study includes five leading academic cancer research centers. The BBD will coordinate the samples, data, analysis, and publication of data. More assessments are planned and will include additional materials and laboratories.

The BBD also serves as a reference laboratory for the National Institutes of Health (NIH) project on the development of RMs for validation of clinical measurements of ctDNA in cancer patients. This

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<sup>11</sup> NIST, Cell Systems Science Group, <https://www.nist.gov/material-measurement-laboratory/biosystems-and-biomaterials-division/cell-systems-science-group>, accessed September 25, 2017.

project has been approved, and is now in the proposal development and funding stage. Working group members include stakeholders in pharmaceutical companies, the FDA, the College of American Pathologists, the American Society of Clinical Oncology, the NCI, the NIH, the Association for Molecular Pathology, and NIST.

As part of the BBD's engineering and synthetic biology-related activities, the BBD is also working to develop standardized measurement assays and reporting characteristics for genetic circuit elements. It is also working to establish reference strains and materials to support predictive design—by ensuring comparability of data between different research laboratories and by enabling absolute quantitation of engineered biological functions. The measurement methods that the BBD is developing include flow cytometry, single-molecule RNA-FISH (a single-molecule counting approach that has enabled the BBD to demonstrate measurements of the number of mRNA molecules in each bacterial cell<sup>12</sup>), as well as other quantitative microscopy approaches.

The BBD research has led to more quantitative measurements for the performance of engineered microbial organisms. This will ultimately lead to improved predictability and reduced trial-and-error in the engineering of biology. It has also developed measurements to characterize the growth and phenotype of genomically minimized bacterial strains during the genome minimization process. Additionally, it is developing predictive capability with genome scale modeling to address questions regarding the sensitivity of promoter activity to the biological response of cells to changes in the environment. It is also supporting Defense Advanced Research Projects Agency (DARPA) in high risk program development through a staff detail.

### **Opportunities and Challenges**

With the awarding of the Manufacturing USA Institutes, NIIMBL, and the Advanced Tissue Biofabrication Manufacturing Innovation Institute (ATB-MII), and the passage of the 21st Century Cures Act, the active role that the BBD division has been playing in supporting regenerative medicine products is poised to ramp up even more. Stakeholder interest in NIST's contributions to regenerative medicine products has been increasing rapidly over the past few years, but these new activities specifically tag the BBD with additional responsibilities. BBD leadership is needed in laboratory activities that advance measurement science in this field, in educating and coaching practitioners on how to apply measurement assurance principles and materials in their facilities, and in working with them on the development of standards. BBD stakeholders include academic research laboratories, cell manufacturers, biotechnology and pharmaceutical companies, instrument and equipment manufacturers, the FDA, and other federal agency partners. The BBD is working with these communities in several diverse, but related, activities, including cell characterization assays, flow cytometry, microbiome, and genomic editing evaluation.

Since increased federal funding is not predicted, the BBD is looking toward forming collaborations and consortia with instrument manufacturers (such as the producers of cell counting instruments and flow cytometers); developers of ancillary materials and therapies (including establishing a consortium with many of the companies developing or using genome editing technologies); the FDA (by collaborating with them to address their responsibilities dictated by the 21st Century Cures Act and in standards development); and research laboratories—particularly in the CAR-T cell therapy area. Consortia and collaborations will hopefully provide resources and enhance impact. Additional federal funding would increase the efficiency with which the BBD can provide these services.

The NIST Strategic and Emerging Research Initiatives (SERI) program provided two-year funding that helped to initiate a technically advanced and scientifically sophisticated program on engineering biology. That funding has allowed several successes to be achieved. Significant laboratory and modeling

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<sup>12</sup> A.K. Neilsen, B.S. Der, J. Shin, P. Vaidyanathan, V. Paralanov, E.A. Strychalski, D. Ross, D. Densmore, and C.A. Voight, Genetic circuit design automation, *Science* 352(6281):aac7341, 2016.

collaborations with the J. Craig Venter Institute, Massachusetts Institute of Technology (MIT), and the University of Maryland (UMD) were established. Two significant co-authored publications have appeared in *Science*.<sup>13</sup> A robust internal program of advanced measurements and theory for engineering biology has been initiated. This program, while currently focused on the analysis and modeling of bacterial systems, has wider implications that include mammalian systems. And so it has potential to greatly impact synthetic biology and regenerative medicine.

The MML is working with the Physical Measurement Laboratory (PML) to identify pan-NIST interests and develop cross-divisional programs in biological-related measurement science. Two areas of synergy include expertise in imaging and interest in precision medicine. The MML has significant work in imaging at the cellular and subcellular scale, and PML has advanced expertise in medical-scale imaging—including phantom development for MRI and other clinical modalities. To help establish collaborative projects that could be built on a request for additional budget authority, NIST's MML, PML, the Information Technology Laboratory (ITL), and the Center for Nanoscale Science and Technology (CNST) units are holding a workshop to bring NIST scientists together to discuss ongoing and future work in imaging technologies. Bringing the various laboratories within NIST together (there are already significant interactions between MML and ITL in imaging) will expose those technical opportunities that NIST is uniquely positioned to tackle. This effort is in anticipation of a future NIST initiative in precision medicine.

A major challenge is to bridge the intellectual and lexicon gaps between biological needs and physical science capabilities. Although imaging has been identified as an important crosscutting area for the PML and MML laboratories, it will be critical to identify what other crosscutting areas may exist between the laboratories. Having staff members serve as liaisons between the laboratories has been useful for identifying potential in-house collaborations. More postdoctoral support may be required to focus on the powerful measurement science that could emerge from these two laboratories. It is critical for the BBD to productively engage other laboratories at NIST in biorelated activities for two reasons: (1) to take advantage of advanced technological capabilities at NIST in order to address unmet measurement needs in biology, and (2) to increase the appreciation and understanding of the role that NIST needs to play in supporting measurements of biological systems.

Additionally, given the observed high-content and high-throughput biodata (in matter genomics, next generation sequencing, and synthetic biology) that is being generated and accumulated by the BBD, the division needs to expand its working relationships with other NIST divisions that focus on informatics, specifically within the ODI.

A combination of a hiring freeze and anticipated severe reduction in funding will have substantial impact on NIST's ability to serve stakeholders, carry out its mission, and retain an engaged workforce that can carry out state-of-the-art technical research in measurement science. Since the budget scenario for FY 2018 and on is still largely theoretical, it is difficult to project what responses need to be prepared for. At the moment, the BBD is reviewing programs to identify the highest priorities in a climate where priorities may be changing. Every research area for which the BBD is developing standards, measurement science, and validation of methodology is of great value to the biological and life science arenas.

The ability to identify and retain excellent scientists who can be engaged in interdisciplinary research, including engineers, statisticians, physicists, chemists, and biologists, will be critical to navigate this rapidly advancing field, leverage NIST-wide expertise, and manage resource challenges.

Initiatives that support biological measurement science are not the most widely supported at NIST. Biological measurement science has the potential to be highly impactful in the coming decades, but translation from basic research to application requires strong biological measurement science and reliability.

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<sup>13</sup> These two publications were: Hutchison, C. A. et al. "Design and synthesis of a minimal bacterial genome" *Science* 351, (2016) and Nielsen, A. A. K. et al. "Genetic circuit design automation" *Science* 352, 53+, (2016).

The microbiome field, as tested by NGS technologies, is challenging given the multitude of testing and informatics analyses pipelines, and such challenges present an opportunity for the Microbial Metrology Group to improve cohesiveness and develop standards. The Microbial Metrology Group and the Biomaterials Group have developed advanced measurements and standards for human pathogen detection and have been valuable partners for the FDA and the DHS by providing NIST mixed microbial DNA RMs and *S. cerevisiae* NE095 in lieu of biothreat agents. Recent advancements in microbial research supports the idea that the human microbiome plays a major role in human health and disease and represents an understudied diagnostic and therapeutic target. The group is well positioned to provide standards materials and methods to promote human microbial detection as diagnostic and therapeutic biomarkers.

The JIMB, partnered with Stanford University, has many opportunities for collaboration with small and large biotechnology companies in the San Francisco Bay Area, which are diverse and numerous. This group can serve as a conduit for many NIST laboratories that are considering locating staff in the Bay Area to leverage the fast-paced technology development there. The opportunity to hire postdoctoral researchers from Stanford and other eminent research universities to work for NIST, without their having to relocate to the East Coast, provides an advantage with respect to bringing in new talent from the West Coast. This advantage, however, comes with the higher cost of living in the Bay Area.

The BBD noted that there is an urgent need for standard materials for testing and/or calibrating deep-sequencing equipment, procedures, and analyses. In collaboration with their stakeholders (federal agencies or industrial partners), the BBD needs to expedite the development of RMs pertinent to NGS-based biomarkers for precision medicine. Such RMs could be used in diagnostic, prognostic, and predictive markers for therapy. These RMs could also be utilized to assess the metrological and analytical sensitivity and specificity for disease detection and classification (e.g., circulating tumor DNA reference materials).

## **PORTFOLIO OF SCIENTIFIC EXPERTISE**

### **Accomplishments**

Based on the recent developments by the BBD technical groups, as outlined in the previous sections, the BBD evinces scientific expertise on par with that of leading researchers in the areas being researched and developed. The BBD appears to have deep technical expertise in the measurement of biological systems and is developing the same capacity for bioengineering. The caliber of the science being performed at the BBD is excellent. The staff members are very motivated, highly trained in their respective fields, and enjoy working at NIST. The groups are working well together, and morale appears to be high. They choose programs and projects in a strategic manner by integrating strong stakeholder input and aligning outside capabilities to their internal strengths. A good example is the JIMB collaborative program at Stanford University on advances in biological and medical measurement.

The group leaders appear to communicate and work well together. They are respected and admired by the scientists and technicians at the BBD. Their knowledge of what is going on in many fields and their network of scientists outside of NIST is impressive. They know that they have to attend external meetings, deliver presentations, and publish as well as patent their findings. There is a can-do atmosphere, especially on the innovation and entrepreneurial bench-to-bank side of the equation, to meet societal needs.

The Microbial Metrology Group is highly visible and represents NIST on the Fast Track Action Committee on Mapping the Microbiome that was organized and hosted by the White House's OSTP. The group has the expertise and connections to fulfill the unmet need for standards and RMs to increase interlaboratory comparability and confidence in microbiome measurements.

The Bioassay Methods Group is highly trained and motivated to bring quality assurance and quality control standards and methods for both qualifying and quantifying biological activity, wellness, and

disease. This group has impressive researchers who are doing cutting-edge research. They effectively collaborate within and outside of the group to leverage needed talent.

The Biomaterials Group is focusing on areas that are cutting-edge in bioimaging and biotechnology. The group possesses a highly qualified staff and a strong external network of collaborators at federal agencies and in industry and academia. The group is poised to develop, and potentially commercialize, rapid BCARS microscopy of cells, tissues, and materials.

The Cell Systems Science Group has a focus on the cell as a system and tools in medical research, and is at the center of many of the major research programs being undertaken by NIST, NIH, and pharmaceutical and biotechnology companies. The group has extensive expertise in developing measurement tools and protocols to ensure the reliability and comparability of cellular and imaging assays.

Some noteworthy examples of Department of Commerce (DOC) and NIST-named awards won by the BBD staff include the 2015 Bronze Medal for establishing reliability in flow cytometry measurements to improve clinical disease diagnosis, cell therapy manufacturing, and biomedical research, and the 2014 Bronze Medal for the development of a “clinically relevant measurement and standardization program for the critical evaluation of photo-polymerized dental restoratives.”<sup>14</sup> One external award won by the BBD was the 2016 Judson C. French Award for the development of the first ever cancer gene copy number diagnostic SRM, NIST SRM 2373. Additionally, one of the JIMB bioengineers was recognized in January 2017 with a Presidential Early Career Award for Scientists and Engineers (PECASE).

### **Opportunities and Challenges**

The JIMB establishes a footprint of NIST on the West Coast and will attract new talent to work on genomic metrology, which is in great need of RMs, measurement science, and validation. The highly creative and trained NIST group at Stanford continues to try to include the NIST staff at the Gaithersburg campus in many platforms and in developing and expanding their capabilities.

Key technical expertise in specialized instrumentation has been lost and not replaced. There needs to be concerted effort to maintain continuity in the staffing of critical positions within the BBD.

## **ADEQUACY OF FACILITIES, EQUIPMENT, AND HUMAN RESOURCES**

### **Accomplishments**

The BBD laboratories that were visited during the review are well-stocked with the latest and best equipment for doing research in biotechnology. In addition, the scientists are very good at tweaking the instruments to do more, and at integrating systems and creating new instruments. Biotechnology is a rapidly evolving technology, and the BBD has been trying to anticipate emerging measurement needs, in addition to hiring and training experts to provide results that have an impact in biotechnology standards and measurements. The division has overall done an excellent job of acquiring the best tools in their respective space to advance the understanding of complex biological systems on many fronts and at many levels.

The facilities visited were designed for maximum output and were very well kept with respect to clean laboratory benches, well-stocked supplies, and a good flow of laboratory capabilities. The equipment of the BBD is state-of-the-art. However, some laboratory infrastructure is not adequate for

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<sup>14</sup> NIST, “National Institute of Standards and Technology Presents 2014 Awards to Outstanding Employees,” updated August 15, 2016, <https://www.nist.gov/news-events/news/2014/12/national-institute-standards-and-technology-presents-2014-awards>.

conducting particular experiments, such as a cell culture up to Biosafety Level 2 (BSL-2) standards. This is owed, in part, to aging building infrastructure and excess storage in laboratory space.

Additionally, equipment purchases are difficult, in part due to an institutional overhead for equipment of 50 percent. This equipment tax significantly reduces the amount of equipment that the BBD can purchase. Given that the tools in the biotechnology space are continually being redesigned for more quantitative analysis in order to remain competitive, purchasing new equipment or retrofitting existing equipment will be high on the BBD investigators' list. Partnering with instrumentation companies is something that the BBD already does extremely well. It is important that it continue to seek companies that have developed the next generation of biotechnology tools for alpha and beta testing and obtain the instruments at a reduced cost.

With respect to human resources, the BBD is a highly productive division. It is effective and efficient regarding output, especially considering it has such a lean staff. The BBD manages to achieve its stated objectives with its small staff, diverse thrust focus areas, four major programs, and its role in the JIMB. The ratio of Ph.D.'s to technicians is high, and in some applications more technicians could be employed to carry out some of the required maintenance of reference standards. The BBD management needs to consider adding more staff to the four divisions if it is going to continue to lead. It also needs to consider forming strategic partnerships for measurement standards, RMs, and validation within the many and varied areas of biotechnology.

### **Opportunity and Challenges**

Working mainly in the biotechnology arena, the BBD has both challenges and opportunities. This unique group of scientists (whose expertise includes biology, chemistry, mathematics, computation, engineering, and physics) is addressing the complex biological sciences that are continually in flux and driven both by policy and regulatory issues that seem to change frequently.

Recognizing that there is a need for better measurements and standards for data sharing, reproducibility, scale-up, and commercialization, the BBD is working on the right things at the right time. For example, it is working in metagenomic microbial measurements, genomics standards, cell manufacturing and therapies, synthetic biology, and predictive biology. However, given the broad space of biological systems, a critical mass of staff and resources may hinder the pace of development that some of these areas demand. Additionally, with respect to human resources, there appear to be some delays in the replacing of critical staffing positions.

## **DISSEMINATION OF OUTPUTS**

### **Accomplishments**

The BBD has hosted a series of NIST-led workshops aimed at engaging with key stakeholders to identify pressing measurement challenges in the regenerative medicine and advanced therapies sectors. These workshops were the *Strategies to Achieve Measurement Assurance for Cell Therapies Products Workshop* (May 2015); *CAR-T Biomanufacturing Symposium* (February 2016); *Genome Editing Standards Workshop* (May 2016); and the *NIST-FDA Cell Counting Workshop* (April 2017).

The *Standards for Microbiome Measurements Workshop* was jointly hosted by NIST, the NIH National Institute of Allergy and Infectious Diseases (NIAID), and the Human Microbiome Project (HMP) in August 2016. The Microbial Metrology Group played a leading role in the workshop, which assembled microbiome researchers from federal agencies, academia, and industry in a precompetitive space to prioritize needs and form an action plan to move microbiome standards development forward. The workshop began as an effort to gather input on defining RMs, reference data, and RMs for human microbiome community measurements. While the scope of the workshop was applicable for anyone



involved in microbiome-based R&D, there was an emphasis placed on DNA-based measurements of the human microbiome as it pertains to the development of new clinical diagnostics, microbiome therapeutics, epidemiological investigations, and the associated regulatory challenges.

NIST also hosted a series of three workshops—the NIST-FDA *Standards for Pathogen Detection Workshop*—over the last 3 years, which were also organized by the Microbial Metrology Group. These workshops have focused on standards for pathogen detection and identification and on the use of NGS technologies for clinical diagnostics and biothreat detection. The consensus outcome from the NIST-FDA workshop on microbial NGS-based standards for pathogen detection was for NIST and the FDA to jointly develop a mixed pathogen RM and associated data that will allow the community to assess the performance of their microbial detection systems and enable regulators to vet the performance claims made by the laboratories and companies creating and using these systems. NIST will be hosting its fourth workshop in this series in the summer of 2017, and that workshop will focus on the clinical diagnostics for infectious disease and biothreat detection communities.

As previously mentioned, the JIMB has also held several public workshops that have highlighted the need to understand the quality of results from next-generation sequencing (NGS).

The division has been very productive, with over 140 publications that include top scientific journals such as *Science* and *Nature*. These high-impact publications reflect a substantial contribution of BBD scientists in consortia and collaborative groups. Standards activities count the release of 16 SRMs/RMs, 8 SRDs, participation in 44 standards committees, 6 awarded patents (and 11 patents pending), and a number of leadership positions.

The BBD's engineering and synthetic biology-related activities have produced 148 archival journals, 23 conference proceedings, 23 NIST reports, 13 books, and 7 book chapters. Some noteworthy examples include the following:

- Hutchison, C.A., Chuang, R., Noskov, V.N., Assad-Garcia, N., Deerinck, T.J., Ellisman, M.H., Gill, J. et al. 2016. Design and synthesis of a minimal bacterial genome. *Science*, Volume 351, Issue 6280, aad625, DOI: 10.1126/science.aad6253. This paper reports a systematic process of genome minimization, so that a bacterium is engineered to have only 473 genes—the smallest genome of any freely living organism. This organism is an important milestone in biotechnology and evolutionary biology, because it provides a simplified platform to add genes back into the genome one by one to study their effects.
- Nielsen, A.A.K., Bryan S. Der, B.S., Shin, J., Vaidyanathan, P., Paralanov, V., Strychalski, E.A., Ross, D. et al. 2016. Genetic circuit design automation. *Science*, Volume 352, Issue 6281, aac7341, DOI: 10.1126/science.aac7341. This paper describes a programming language, called Cello, for cellular logic to compile high-level functional specifications into DNA sequences that can be inserted into bacterial cells, giving them new sensing and response capabilities.
- Camp C.H., Lee Y.J., Heddleston J.M., Hartshorn C.M., Hight Walker A.R., Rich J.N., Lathia J.D., Cicerone M.T. et al. 2014. High-speed coherent Raman fingerprint imaging of biological tissues. *Nature Photonics* 8:627-634, DOI: 10.1038/nphoton.2014.145. This paper describes the development of a new BCARS microscopy platform that acquires spectra with unprecedented speed, detection limit, and spectral breadth.
- Elliott J.T., Rösslein M., Song N.W., Toman B., Kinsner-Ovaskainen A., Maniratanachote R., Salit M.L. et al. 2016. Toward achieving harmonization in a nano-cytotoxicity assay measurement through an interlaboratory comparison study. *ALTEX*, 34(2):201-218. doi: 10.14573/altex.1605021 This manuscript illustrates the application of advanced measurement science tools such as in-process controls and interlaboratory comparisons to a conventional MTS (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium) cell viability assay protocol.
- Stulberg, E., Fravel, D., Proctor, L.M., Murray, D.M., LoTempio, J., Chrisey, L., Garland, J., et al. 2016. An assessment of U.S. microbiome research. *Nature Microbiology*. Article number:

15015, doi:10.1038/nmicrobiol.2015.15 This paper summarizes the assessment of the status of U.S. microbiome research by a team of governmental scientists from fourteen governmental organizations. This study has implications for the funding of future microbiome research, in both the United States and internationally.

The BBD has also disseminated key position papers on measurement assurance strategies, including perspective papers in *Cell Therapy* and *Stem Cells Translational Medicine* on quality attributes for cell therapy products and on improving measurement assurance.

Outside of workshops, some of the BBD's impact includes delivering measurement solutions to Lonza, a leading cell contract manufacturing organization, to enable comparison cell enumeration by automated and manual methods. The BBD's customer outreach includes collaboration with Chris Voigt's laboratory at MIT to develop measurements and reference objects for synthetic biology. As mentioned, they also have collaborations with the J. Craig Venter Institute and MIT to characterize the phenotype of genomically minimized cell strains and to inform the potential for the minimal cell to serve as a tool for fundamental research and biomanufacturing.

The BBD has also elevated NIST's profile through its regenerative medicine-related activities, specifically through the administration of the U.S. Technical Advisory Group (U.S. TAG) for ISO/TC276: Biotechnology, as well as through their leadership in ASTM FO4 on Tissue Engineered Medical Products. The U.S. TAG to ISO/TC276 Biotechnology group is a way for NIST to coordinate national and international standards activities for existing and emerging biotechnology sectors. The primary goal of this technical advisory group is to enhance the global competitiveness of U.S. business and quality of life by promoting and facilitating voluntary consensus standards and ensuring their integrity in biotechnologies. It has developed innovative approaches for evaluating the quality of cell counting measurements through experimental design and statistical analysis. These methods have been implemented by industrial and academic clinical centers to improve the confidence of their critical cell counting measurements and are the basis for an international standard under development in ISO TC 276.

As part of its regenerative medicine-related activities, the BBD has also presented webinars and high-profile lectures to key industry and regulatory stakeholders. It has also established a Memorandum of Understanding (MOU) with the Standards Coordinating Body (SCB) for gene, cell, and regenerative medicine and cell-based drug discovery in order to coordinate standards development for regenerative medicine and advanced therapies.

The BBD's engineering and synthetic biology-related activities include strong customer engagement. In partnership with the American Type Culture Collection (ATCC) and other consortium members, the BBD is working to design tools, establish data sets, and further develop and standardize NIST's patented authentication method through the use of NIST-identified short tandem repeat (STR) markers for mouse cell lines. The goal is to develop a commercially available assay kit based on the STR markers and the method for mouse cell line authentication.

NIST is also collaborating with manufacturers of microparticles to develop RMs. These include reference fluorophore solutions and biological RMs. They also include reference data and RMs for assigning an equivalent number of reference fluorophores (ERF) values, and assessing the associated uncertainties and utilities.

The BBD also established interagency agreements between NIST and other federal agency partners: NCI/EDRN; DHS; DARPA; NIH/National Institute of Dental and Craniofacial Research (NIDCR); and the FDA. A Memorandum of Understanding (MOU) was established between NIST and the SCB for gene, cell, and regenerative medicine and cell-based drug discovery to help coordinate standards development for regenerative medicine and advanced therapies.

NCI's clinical trials reference laboratories have used NIST SRM 2373 to improve the confidence of the human epidermal growth factor receptor 2 (HER2) Gene Copy Number. This SRM has enabled test manufacturers and pharmaceutical companies to produce the secondary RMs required to ensure accurate and reliable clinical measurements of HER2.

The National Renewable Energy Laboratory (NREL) is also using NIST-developed technologies for the measurement of metabolites in processes that employ engineered organisms to convert corn stover to useful chemical products. The BBD is working with the NREL to facilitate this transfer of capabilities.

Another BBD dissemination activity has been through the NIST SRI Program Standard Reference Instrument (SRI) Tensometer, which is a cantilever beam-based tensometer to measure the polymerization stress, polymerization exotherm via temperature monitoring, degree of conversion, and kinetics. This instrument has been made available to industry and university researchers through the NIST SRI program. In addition, NIST has conducted measurements for recent NIDCR U01 grantees to ensure comparability of results. This method is also under consideration as an international standard or technical specification through ISO/TC106 Dentistry.

Some noteworthy examples of BBD's 17 patents and patents pending include the following:

- J. Almeida and K. Cole. 2016. U.S. Patent No. 9,556,482: Mouse Cell Line Authentication. An authentication method using NIST-identified noncoding STR markers.
- M. Halter Peterson and A. Plant. 2015. U.S. Patent No. 20150168300 A1: Article and Process for Modifying Light. This invention enables high spatial resolution surface plasmon resonance imaging (SPRI) through a microscope objective, where no commercialized product yet exists. SPRI allows for the measurement of intrinsic physical properties of materials (refractive index, mass, thickness) at a surface interface in a real-time, label-free format.
- J. Elliott and A. Christopher. 2016. Non-Provisional U.S. Patent Application: Process for Making an Asymmetric Fluorophore. This invention relates to a process for synthesizing a small molecule asymmetric boron-containing fluorophore. The asymmetric fluorophore was designed to aid in cellular membrane permeability while retaining aqueous solubility. The fluorophore can be conjugated to proteins within live cells or fixed cells and provides whole-cell staining of such cells.

The BBD also maintains leadership of and contributions to roadmaps, planning groups, and policy forums including the National Academies of Sciences, Engineering, and Medicine's Regenerative Medicine Forum and the National Cell Manufacturing Consortium (NCMC). They also interface with the NIIMBL, which is funded by the DOC and the Department of Defense (DOD) Advanced Tissue Biofabrication Manufacturing Innovation Institute-awarded Advanced Regenerative Manufacturing Institute (ARMI).

Their leadership positions in relevant societies and organizations include the Society for Biomaterials, Tissue Engineering and Regenerative Medicine International Society-Americas (TERMIS-AM), ASTM, and ISOs. They also contribute to interagency activities through the Multi-Agency Tissue Engineering Science (MATES) Working Group with the NIH, FDA, DOD, NSF, and the White House OSTP. They will be assuming the chair of this working group in spring 2017.

The BBD also helped to nucleate and participate in IMMSA, which was founded to identify and disseminate developments related to improving microbiome measurements. The Microbial Metrology Group participated in this alliance.

## **Opportunities and Challenges**

One concern is that the BBD has a relatively limited reach in its communication with a broad customer base and with its stakeholders. While the BBD has developed websites (its current website reflects a significant improvement from its previous one), held workshops, and creates and contributes to consortia, stakeholder outreach currently remains limited, and the BBD needs to pursue and explore mechanisms for reaching its stakeholders.

## Chemical Sciences

### INTRODUCTION

In achieving the overarching goals of National Institute of Standards and Technology (NIST) and the Material Measurement Laboratory (MML) for measurements on complex chemical systems, the Chemical Sciences Division (CSD)<sup>1</sup> provides an essential set of tools for the work of all chemical scientists and engineers, contributes to a large segment of the nation's production of goods and energy, and enables quantitative measurements of the contents of the atmosphere and waters that can provide warnings when impurity levels in the air or water may negatively impact the health of Earth's natural environment and its inhabitants. A concise statement of the CSD mission is as follows:

Supports future developments in the chemical sciences by creating state-of-the-art chemical measurement capabilities, theories and computational methods for quantitative measurements, and methods for sensing of solids, liquids, gases, plasmas, transient species, and multicomponent matrices. The division also formulates and disseminates reference materials and critically evaluates reference data used in a wide range of applications, including chemical manufacturing, clinical health assessment, food and nutritional assessment, and exposure science.<sup>2</sup>

For most of a century NIST's compilations of evaluated chemical data, structures of molecules and materials, spectroscopic and thermochemical properties, and mechanisms and rates of chemical reactions have provided essential tools for the work of almost all chemical scientists and engineers.

The CSD works in partnership with other organizations within NIST, with other government laboratories, and with institutions throughout industry and academia. This optimizes the creation and dissemination of new, state-of-the-art technologies, which enables chemical science, technology, and engineering enterprises. It encourages innovation and provides the basis for high confidence levels in measurements and technologies that are used in a wide range of applications. These applications include chemical analyses and separations that support environmental stewardship, health care diagnostics and therapies, detection of explosives or poisons, and advanced chemical and solid-state device manufacturing (and much more).

The CSD staff is approximately one-fifth the size of the MML's and is comparatively as large as the MMSD and MSED, which each make up 19 percent of the MML. The staff members include 8 office staff and eight technical groups that range in size from 8 to 36 members and work over a broad range of scientific and engineering areas. These groups are the Chemical Informatics Research Group, the

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<sup>1</sup> Some of the background information within this chapter was derived from the document NIST, "Made to Measure—Building the Foundation for Tomorrow's Innovation in the Biological, Chemical, and Materials Sciences," pp. 131-152, 2017.

<sup>2</sup> NIST Material Measurement Laboratory, "Made to Measure: Building the Foundation for Tomorrow's Innovation in the Biological, Chemical, and Material Sciences," read-ahead to the panel, May 9, 2011, p. 13.

Chemical Process and Nuclear Measurements Group, the Environmental Chemical Sciences Group, the Environmental Specimen Bank Group, the Gas Sensing Metrology Group, the Inorganic Measurement Science Group, the Marine Biochemical Sciences Group, and the Organic Chemical Measurement Science Group. The eight CSD groups contribute to its five division-wide program areas in chemical sciences for biomedical and health research and applications, nutrition science, advanced chemical metrology for natural resources monitoring, atmospheric chemical sciences, and advanced chemical manufacturing.

There are 8 people providing administrative support with an average load of 22 technical staff members per person. There are also 13 technical staff members that have some managerial responsibilities. The CSD facilities are located in Gaithersburg, Maryland, with the exception of 30 people at the Hollings Marine Laboratory (HML) in Charleston, South Carolina, and one person in Hawaii.

## ASSESSMENT OF TECHNICAL PROGRAMS

### Accomplishments

The Inorganic Measurement Sciences Group conducts research on the measurement science that underpins the identification and quantification of inorganic chemical species in support of manufacturing and environmental stewardship. Additionally, the group develops, critically evaluates, and applies an unusually broad range of analytical methods. It also

Investigates fundamental physical and chemical processes to develop new analytical techniques and to improve existing analytical methodology; applies the results of this research to the certification of SRMs and other RMs important to U.S. industry and government agencies; maintains and develops inorganic SRMs for commodities and for calibration of basic chemical quantities including: pH, electrolytic conductivity, and concentration; provides advice and measurement services; and serves on the committees of eighteen international standards organizations.<sup>3</sup>

The scope and significance of this group's projects are striking. The Avogadro project, which is pursued in collaboration with several other national standards institutions, is designed to measure the Avogadro constant, about  $6 \times 10^{23}$ , to an accuracy of 20 parts per billion, and to redefine the kilogram as of next year in terms of Planck's constant. The standard kilogram in Paris will then be the final physical artifact to be retired from service as a fundamental SI base unit.

Its work on the creation of pH standards for the ocean and other high-ionic-strength environments is particularly impressive. At the high concentrations of salts in the ocean, the chemical potentials of water and indicator dyes, and of their ions, are shifted from those in pure water by the presence of near-neighbor ions. This significantly alters apparent pH. Such research requires a deep understanding of complex chemical processes, meticulous and systematic design, execution in the laboratory, and a thorough and sophisticated analysis of the generated data. This is an impressive piece of research. These standards are critical for important industrial processes and required for measuring ocean acidification over the years. These standards are also important for anticipating industry impact on ocean life, on the environment, and on the resources available to humans.

It is also working on the production and documentation of long-lived standard reference materials (SRMs) for pure inorganic and organometallic materials, for single-element and single-anion solutions, and for many practical materials such as alloys, cements, nanomaterials, and catalysts. It is providing highly reliable standards that are important in a wide range of industries and research laboratories. This

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<sup>3</sup> Ibid., p. 132.

major and sophisticated effort makes extensive use of NIST's broad range of powerful analytical tools and is clearly excellent work.

Engineered nanoparticles (ENPs) have started being produced and used in an empirical way on an industrial scale for many types of products and processes. This group is developing a suite of methods for defining the physical and chemical properties of these particles as they are synthesized and prepared for application. It is also starting to study the release of ENPs from commercial products and the potential for environmental health and safety consequences of their release during both the manufacturing and the use of products containing ENPs.

The Organic Chemical Measurement Science Group quantitatively evaluates and then improves methods for the identification, quantification, and traceability of organic species. It has built up a laboratory with modern analytical equipment based on at least seven different molecular properties. From a knowledge of the fundamental principles of each method, of the variation in properties of types of analytes, and of the resolving power of different chromatographic substrates and changes in instrument designs, the group improves the resolution and sensitivity of its instrumentation to meet programmatic needs—or designs new methods as required. Based on this work, the group provides critically evaluated RMPs, 29 for biomedical and health research alone, as well as 250 SRMs. It also provides advice and measurement services to U.S. industry and manufacturing, federal and state government agencies, and scientific organizations. It interacts with international standards organizations and other National Metrology Institutes to establish comparability of measurement capabilities. This year, a fundamental chemical metrology standard, NIST PS1: Primary Standard for Quantitative NMR (Benzoic Acid) will be released as the highest metrologically ordered standard for SI traceability of organic chemical measurements. The benzoic acid is  $99.992 \pm 0.005$  mass fraction percent pure.

Additionally, the Organic Chemical Measurement Science Group is providing standard substances to law enforcement for training dogs to smell explosives and illegal drugs and is setting up a Novel Psychoactive Substances Data Hub. It also contributes to crosscutting programs in nutrition science, metabolomics, and biomedical and health research.

The Gas Sensing Metrology Group is responsible for

Critically evaluating, developing, and applying high-accuracy, amount-of-substance measurement techniques, generating reference data and the dissemination of SI-traceable standards for the identification and measurement of gaseous species in atmospheric media (urban, rural, and pristine), process streams (automobile and stack emissions), and long-path observations (remote sensing and greenhouse gas monitoring).<sup>4</sup>

It has developed state-of-the-art laser spectroscopy equipment for detecting and quantifying trace gases down to a fraction of a part per trillion. This is a substantial advance in the science and technology of trace gas detection and measurement. Its power is dramatically exemplified by the measurement of <sup>14</sup>C (~5000 year half-life) carbon dioxide concentrations to distinguish combustion products from modern carbon sources, such as cornstalks or biofuel (1 parts per billion [ppb]) or from fossil fuel (coal or oil, 0 ppb). The instrumentation is now working and is being developed for field studies. Once patented, it will be suitable for commercial production. It promises to replace the much more expensive and bulky accelerator mass spectrometric technology and make these <sup>14</sup>C measurements more widely available and less expensive.

Accurate spectroscopic measurements of concentrations of gases using satellites (e.g., for atmospheric greenhouse gases) or ground-based lasers (e.g., aimed through stack gas plumes or automobile exhausts) require precise measurements of line positions and line shapes as they are broadened by collisions with ambient gas molecules. Using the Gas Sensing Metrology Group data, molecular collision theorists have successfully verified methods for calculating line-shapes, so that the detailed laboratory measurements are not required for every possible ambient gas and temperature (e.g.,

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<sup>4</sup> Joseph T. Hodges, NIST, "Gas Sensing Metrology," presentation to the panel on May 9, 2017, p. 2.

flames). These molecular concentrations are then used directly by atmospheric modelers. The group has already provided the key spectroscopic data for six of the most important atmospheric molecules. It also standardizes equipment for atmospheric ozone and mercury measurements.

The methods, data, and services provided by this group are critical enablers of the measurements of atmospheric gases that monitor air pollution and the progress of global warming. The data from these measurements allow predictions of the long-term impacts on the environment and existing populations and therefore provide a basis for national and international policy-making and corrective action. Both the quality of the scientific work and its importance to humanity strengthen NIST's position as a leader among international standards-setting institutions.

The group is also in the process of developing another half-dozen promising optical sensing technologies for air metrology of our changing atmosphere. Their development of optical sensing technologies includes a focus on frequency-stabilized cavity ring-down spectroscopy, frequency-agile rapid scanning spectroscopy, photoacoustic spectroscopy, and multi-heterodyne spectroscopy with optical frequency combs. One patent has been awarded and another is pending for these novel applications of optical devices.

The production of SRM gas mixtures in cylinders containing accurately known and traceable compositions is an important program that supports research, environmental monitoring, and industrial production. For example, carbon dioxide (CO<sub>2</sub>) concentrations in mixtures for greenhouse gas calibration are determined to  $\pm 0.1$  ppm at 400 ppm. SRMs are prepared from >125 different gases and, during the previous 6 years, annual gas SRM sales fluctuated between 283 and 399 cylinders and averaged 328—a bit more than one-quarter of the SRMs produced in the MML.

The Chemical Informatics Research Group develops, validates, and applies methods in computational chemistry (quantum chemistry), molecular simulation (statistical mechanics and thermodynamics), and informatics to study, predict, and evaluate the chemical and physical properties of molecules, gases, fluids, solids, and fluid/solid interfacial systems. It uses the Department of Energy (DOE) advanced supercomputer facilities at the National Energy Research Scientific Computing Center (NERSC) in Berkeley.

The group works closely with experimental groups to explore the underlying mechanisms of observed phenomena and to extend data sets into experimentally inaccessible regions. Two striking examples illustrate how effectively theory can deal with important, messy, and practical industrial problems. Specifically, the group's calculations on high-concentration protein solutions are helping pharma understand how to prepare and administer protein therapies, in which the protein molecules do not form inactive protein clusters and do not fragment when forced through a syringe needle. The group has also taken on the challenge posed by the American Chemical Society (ACS) to reduce the energy intensity of chemical manufacturing industries.

Half of the energy of chemical manufacturing industries is used for distillation—it accounts for 10 percent of the total energy consumed worldwide—a major target for conservation. ACS-organized road mapping workshops identified membrane and adsorbent-based processes as prospects to reduce energy requirements by a factor of 4 to 5. This led NIST and the Advanced Research Projects Agency-Energy (ARPA-E) to add new features to their Adsorption Database. A close and effective collaboration with industry and other laboratories can be expected to strongly accelerate the development of viable processes.

This relatively new group has quickly focused on important applied problems where theory and computation can make a strong contribution. State-of-the-art theory and modeling can guide experimental research and focus pilot plant work in productive directions. The group won a large grant of computer time for the next phase of this work.

The Facility for Adsorbent Characterization and Testing (FACT) laboratory was created at NIST in partnership with ARPA-E. It was created to advance sorption measurement science and techniques for in situ characterization of the bonding of adsorbed molecules in order to enable rational design of new materials optimized for sustainable energy and environmental processes. Specific examples include storage of hydrogen and methane fuels, gas separations for carbon capture or natural gas purification, and

catalytic reactions. A group of 10 universities and businesses is involved in round-robin testing of the reliability of the measurement protocols created in the FACT laboratory.

The Chemical Process and Nuclear Measurements Group conducts “state-of-the-art chemical and physical measurements to advance measurement science and the fundamental understanding of time-dependent phenomena,”<sup>5</sup> such as rate constants, reaction mechanisms, and transport properties. The group has built an extensive array of excellent experimental equipment. They have produced chemical kinetics and photochemical data for use in atmospheric studies that provide the basis for understanding the fate and impact of anthropogenic additions to the atmosphere. Among these additions are the organic molecules that react together, and with oxygen and water, to form “secondary organic” aerosol particles. The group has begun to measure the composition of these particles and to provide analyses of organic aerosol compositions.

It is important to understand the composition of aerosol particles in the atmosphere, how they react chemically, and their impact on human health and the natural environment. This chemistry is very complex and challenging to study. Ultimately, these studies will lead to measurement standards for the quantitative tracking of substances that need to be eliminated and the optimization of human activities that will minimize the detrimental effects of such particles on health and the environment.

The group also provides inorganic analyses of materials used in neutron activation. Recently, it has conducted neutron depth profiling (NDP) to measure, *in operando*, the movement of Lithium-ions (Li-ions) in the solid electrolytes of Li-ion batteries. There are wide-ranging opportunities to expand this work, since solid electrolytes provide potentially higher ionic conductivity, and as a result, better batteries. The anticipated future of emerging technologies in Li-ion batteries using solid electrolytes and the NDP research shows high promise, along with significant scientific challenges. The proposal for three-dimensional (3D) elemental imaging in materials by prompt gamma ray emission tomography will undoubtedly be useful in this project and in many other applications.

The rapid growth of the nation’s use of electrically powered vehicles, the impending introduction of autonomous vehicles, the need for storage capacity on the nation’s electric grid, and the construction of a major Li-ion battery factory make the optimization of this technology an urgent priority. The new instrumentation for observing Li-ions in an operating battery will rapidly accelerate the process. These experimental tools create an opportunity to make major contributions to the national transportation and energy infrastructures, to energy conservation, and to environmental protection. In view of the prospects for major deployment of battery-powered energy and transportation systems, the CSD needs to prepare to fully exploit and share the new tools it has developed for studying and improving the performance of Li-ion batteries.

The HML, founded in 2000, was occupied in 2002 through an agreement between NIST and the National Oceanic and Atmospheric Administration (NOAA), together with the Medical University of South Carolina, the College of Charleston, and the South Carolina Department of Natural Resources. Research at the HML is also supported by the National Sea Grant College Program. The HML is home to the Environmental Specimen Bank Group, the Environmental Chemical Sciences Group, and the Marine Biochemical Sciences Group.

The Environmental Specimen Bank Group’s facility is staffed by 8 NIST scientists who are responsible for developing protocols for the entire operation to ensure that marine samples are collected, transported, prepared, analyzed, and placed in a liquid-nitrogen-cooled storage facility in order to provide data that can be meaningfully compared worldwide and over time. A staff member supervises every step of the process. Ultimately, these materials, combined with those in other facilities, will support work to understand the effects of changes in the environment on marine life forms. As the world’s fisheries become increasingly depleted and fish migrate toward the poles, there will need to be a better understanding of how to manage them, as well as how to design and manage fish farms that produce high-quality seafood. This research fills an important part of the NIST mission.

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<sup>5</sup> Pam Chu, “Chemical Process and Nuclear Measurements Group,” presentation to the panel, May 9, 2017, p. 2.



The Environmental Chemical Sciences Group seeks “to provide measurement science, standards and technology to support the nation’s goals for assessing environmental exposure and effects of natural and man-made chemicals in air, water, soil and biota.”<sup>6</sup> With 11 full-time equivalent (FTE) employees and a few students at the HML, the group has undertaken an enormous set of programs. These programs include (1) performing a complete and extremely important analysis of waste water from hydraulic fracturing—also known as fracking—operations (a subject of intense environmental concern being discussed in the absence of complete data); (2) creating an SRM for the sediment of the significantly polluted Great Lakes to aid in developing monitoring systems and cleanup processes (given the enormous geographical area and its variety of pollution sources and natural environments, sediments from a range of representative locations may be required); (3) developing comprehensive methods for simultaneously determining multiple human hormones from different classes, and creating advanced mass spectroscopic diagnostic methods for clinical disorders of glycosylation using 100 microliters ( $\mu$ Ls) of human blood; (4) measuring, with the Medical University of South Carolina, urinary phthalate metabolites in a racially diverse population of pregnant women; (5) promulgating the use of Serotransferrin (as developed by the group) for a marker of clinical disorders of glycosylation using a proteomics method for screening along with the SI-traceable SRM created for the method; and (6) producing data on the accumulation of Gadolinium (Gd) in the brains of patients examined by MRI using a Gd contrast agent. Another half-dozen projects of substantial interest are also in progress.

The Marine Biochemical Sciences Group’s goal is to perform

State-of-the-art bioanalytical measurements, in order to provide reference data, develop standards, and advance measurement sciences in support of the nation’s needs for knowledge of the identity, quantity and biochemical properties of marine organisms, particularly those that have an impact on human health.<sup>7</sup>

This is clearly a very complex area of major importance. Working with its colleagues, NIST’s group of five at the HML will be able to make valuable contributions. Its project to apply metabolomics metrology in order to assess aquaculture practices deserves emphasis in view of its possible impact on the availability of high-quality seafood for human consumption.

NIST and the University of Colorado created the Joint Institute for Laboratory Astrophysics (JILA) at the Boulder campus in 1962. Following up on this model for preeminent success, the MML has established, since 2000, five similar collaborations: (1) as mentioned, in 2000, the founding agreement for the HML in Charleston, South Carolina, was signed, and the Environmental Specimen Bank Group, the Environmental Chemical Sciences Group, and the Marine Biochemical Sciences Group have been working together with NOAA and three South Carolina institutions since the first labs were completed in 2002; (2) in 2014, the Joint Initiative for Metrology in Biology (JIMB) with Stanford University was launched on Stanford’s Palo Alto, California, campus; (3) also in 2014, the Center for Hierarchical Materials Design (CHiMaD) was formed and located at the Northwestern University campus—it included Chicago universities, the Argonne National Laboratory, QuesTek LLC (a 1997 start-up from Northwestern University that designs specialty metal alloys), and ASM International (a century-old professional society that produces information and data handbooks for the design and manufacturing of metal alloys); (4) in 2010, the Institute for Bioscience and Biotechnology Research (IBBR) was created with the University of Maryland (UMD), on the foundation of the NIST/UMD collaborations in biology that were initiated three decades ago; and (5) in 2017, the newly established National Institute for Innovation in Manufacturing Biopharmaceuticals (NIIMBL) will join the IBBR. NIIMBL is the 11th institute to be created in the Manufacturing USA Network. It is the first of these institutes with a focus area chosen by industry and the first with funding, \$70 million, from the Department of Commerce

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<sup>6</sup> John Kucklick, “Environmental Chemical Sciences Group,” presentation to the panel, May 9, 2017, p. 2.

<sup>7</sup> Frank Mari, “Marine Biochemical Sciences Group,” presentation to the panel, May 9, 2017, p. 2.

(DOC). Other members of the consortium, 103 companies and nonprofit organizations and 41 educational institutions have provided an additional \$129 million.

This expansion of collaborative activities broadens the scope of application of NIST standards and measurements work and strengthens its connections to, and value in, industry. These strategic area partnerships connect NIST to new industries developing in the Middle West and on the Pacific coast, regions previously without a NIST presence. The scope and speed with which these collaborations have been developed is remarkable. The magnitude of the NIIMBL and the industrial connections that it makes available provide an unparalleled opportunity for NIST to accelerate the progress of U.S. industry.

The Chemical Sciences Division (CSD) is continuing NIST's long-established tradition of developing measurement technologies, standards, and essential data to enable progress in industry, engineering, and science. The CSD and the MML are strategically pushing forward on creative and important initiatives. The steady creation of new technologies promises to bring NIST a continuing flow of opportunities to define valuable new standards and methods of measurement in order to make important contributions to the overall progress of science, engineering, technology, industry, and, as a result, to the overall economic productivity and to quality of life.

At this time, the originality, insightful selection of problems, technical prowess, and analysis in exquisite detail exhibited in CSD research is both impressive and essential to the NIST mission. The staff has used, and in many cases created, the most powerful experimental and theoretical tools for advancing its projects. The complexity of the natural systems that it investigates is daunting and the analyses are impressive. That only a few individual projects are discussed earlier is intended to avoid overloading the reader and by no means suggests that the other projects are unworthy. The CSD's contributions continue to support NIST's position as a leader among international standards-setting institutions and serve as an important contributor to national strength in science, engineering, and technology.

### **Opportunities and Challenges**

Batteries are critical components for new technologies and for many ongoing uses in society. Applications are making increasingly high demands on the performance of batteries. When it comes to creating batteries that approach 100 percent efficiency, are safe and rechargeable for years, and are economical and lightweight, there are many complicated chemistry and materials problems that remain to be solved. NIST has a dramatic start to solving such problems through CSD's work on 3D imaging of Li-ions in operating batteries. What roles NIST could play in the future of batteries is a question that needs to be deliberated upon and addressed.

There are many universities and government laboratories in the Washington, D.C., metro area that share interests with NIST. By establishing a regional seminar series or occasional workshops on a topic or set of topics of broad interest (such as atmospheric or marine chemistry) or an efficient, high-quality regional nuclear magnetic resonance (NMR) facility, a group or division could attract researchers and students to visit NIST. Such activities could ultimately develop joint research programs or shared instrumentation facilities, or identify a promising new staff member to recruit. This could be particularly helpful in attracting a more diverse group of candidates for the National Research Council (NRC) Associateship Program and for positions on the NIST scientific staff. NIST's recent track record in research collaborations bodes well for future success in this vein.

In reference to the CSD's collaborations with industry, the CSD staff described the extensive utilization of NIST's standards and data products and listed the industries interested in each project presented. However, it was less clear during the review whether there were temporary exchanges of personnel, or technology transfer by NIST scientists moving to industry, or congressional testimony by industry leaders citing their substantial investment in, or the major impact on, the corporate goals of an NIST project. It was subsequently learned that 1 of the 55 visitors to CSD laboratories came from industry. The number of industry visitors to NIST and NIST staff visits to industry could be substantially

increased. The recent creation of the NIIMBL, with its \$200 million budget, provides a major opportunity for meaningful collaboration between NIST and industry.

In some areas of chemical biology research, NIST is a relatively small contributor. In these areas, collaborations with user communities and publications are particularly important for NIST to become recognized and utilized, and to be able to attract excellent new staff members in chemical biology.

## **PORTFOLIO OF SCIENTIFIC EXPERTISE**

### **Accomplishments**

During the reorganization of the MML four years ago, NIST's chemical sciences expertise was integrated into a single division, the CSD, by combining two groups from the former Chemical and Biochemical Reference Data Division with the Analytical Chemistry Division. This process brought together experts in measurement sciences, RMs, reference data, theory, and chemical informatics. The result of this change is that the division's programs now have a balance between measurement services and fundamental research. During the past 3 years, the division created eight groups in order to solidify technical expertise, optimally satisfy stakeholder needs, take on the nation's technical challenges, and optimize relationships for CSD's crosscutting program areas.

The division's scientific personnel are both talented and productive. They have been recognized within MML, NIST, and the DOC for their excellent professional contributions. The MML Awards Committee organizes the preparation of nominations for a series of internal MML awards, while the MML Accolades Committee accepts nominations from staff, associates, and collaborators.

During 2016, the MML Accolades Committee awarded Accolades to 13 CSD staff members. The CSD has done an excellent job attracting NIST and NRC postdoctoral fellows in chemistry to the laboratories. These fellowships attract applications from the top new Ph.D.'s in the chemical sciences and are rigorously vetted by the National Research Council's experts in their fields. The successful candidates bring fresh science into NIST, are productive during their tenures, and provide an exceptional pool from which to recruit permanent staff members.

### **Opportunities and Challenges**

To be recognized and appreciated by one's colleagues and employer through MML awards is an excellent morale builder. There does not, however, appear to be a systematic process for successfully nominating CSD's scientists for external awards. For the reputation of the institution and its ability to attract outstanding professional staff, to earn recognition in the scientific community nationally and internationally, and to convince funding agencies and corporations of its worth, the CSD could focus on awards and fellowship honors from major professional societies, academies, and foundations. These honors are also important morale builders and quite useful for preemptive retention of star staff members.

As part of this focus, the CSD could establish a committee with an administrative assistant who facilitates and tracks every step of the nomination process for each external award. Since there are many awards (each with its own deadlines, requirements, procedures, and eligible individuals), an awards database could be constructed and maintained for awards that scientific staff members might be eligible for. Prospective candidates would prepare and maintain current descriptions of major accomplishments, a résumé with helpful supplementary materials, and a list of prominent people in the field who could be asked to write a supporting letter. With this information, the committee could identify candidates for nomination. The committee's main charge would be to bring in as many of the best awards as possible to the benefit of NIST. The CSD can do much better for its best staff members. Awards and the presence of NIST fellows enhance the CSD's status within NIST, nationally, and internationally.

Given the outstanding accomplishments of CSD staff members, it was surprising to find that there are no NIST fellows within the division. Currently there are NIST fellows in the ACMD (1), BMD (1), MMSD (3), and MSED (2). The NIST fellow status as well as the DOC medals are important precursors to winning major external awards. It is also a concern that only three of the CSD's eight groups report currently having an NRC postdoctoral fellow—3 in one group, and 1 in each of the two groups. The uneven distribution of these fellows among CSD groups and among MML divisions suggests that only a few people are utilizing the best methods for attracting excellent postdoctoral researchers. The CSD could maximize the number and quality of NIST and the National Research Council Associateship Programs' postdoctoral fellows arriving in CSD through good networking with the university faculty members that produce the best Ph.D.'s in the fields of interest and a systematic process to ensure that attractive projects with outstanding candidates are submitted to the NRC. To identify candidates, the practice of sending letters describing the projects and project leaders to as many leading professors in the field of research as can be identified has been successful.

Systematic networking with university faculty members doing the best work relevant to NIST programs is essential for bringing in outstanding new Ph.D.'s as NIST and NRC postdoctoral fellows. The CSD's relationships with universities through JIMB, CHiMaD, IBBR, and NIIMBL will also create additional recruiting opportunities. This will enable graduate students to come into NIST laboratories for collaborative projects, as well as the hiring of finishing postdoctoral students from university research groups.

The key to creating and maintaining an organization of outstanding and productive scientific professionals is to enable them to do the best work that they can possibly do in their chosen field and to recognize and reward their outstanding accomplishments. The basic requirements are (1) outstanding colleagues who are accessible, are always encouraging and helping each other to do their best, and are able to collaborate when research directions converge; (2) physical facilities that are fully functional and well maintained; (3) the best available equipment with technical staff members who can help create something even better; (4) supportive, experienced, and expert administrative staff members who get equipment and supplies purchased, renovate or alter laboratories to accommodate new work, process grants and contracts swiftly, track and report on budgets monthly, appoint and pay research laboratory personnel, and take care of the many distracting, nonscientific tasks that arrive on the researcher's desk; and (5) a working environment that values and nurtures diversity. These are challenging requirements, especially with buildings in their second half-century of service, a lean support staff, and budgets built more for subsistence than to build excellence. That NIST continues to accomplish important work, including exceptional, groundbreaking progress in science, is a great credit to the organization. Nevertheless, there is ample room for improvement, especially regarding items 2, 4, and 5 in the preceding list.

## **ADEQUACY OF FACILITIES, EQUIPMENT, AND HUMAN RESOURCES**

### **Accomplishments**

The CSD's equipment of all sizes, from National Synchrotron Light Source II (NSLS-II) beam lines to tiny diode lasers, is quite excellent and supports the work of the entire laboratory well. The MML is encouraged to maintain the quality of equipment required to keep the MML state-of-the-art for standards work into the future.

### **Opportunities and Challenges**

The CSD's aging and outdated building infrastructure cannot support the missions of the division and of NIST into the future. Standards work requires flawless performance of the most exacting precision

experiments. With 10 percent of MML space up to modern standard and another 10 percent only modestly compromised, MML researchers have managed to make progress by pasting band aids over problems as they work and by crowding too many instruments into those few spaces that provide proper conditions for sensitive instrumentation. As these buildings and their infrastructures continue to decay, it will become increasingly difficult, expensive, and, for some important purposes, impossible to work. If action is not taken to rebuild these facilities, the most capable staff members will begin to leave NIST—and recruiting scientists that can do this exacting work would become difficult. Ultimately, the nation could lose this institution, which is so vital for its scientific and technological progress. Although it is not possible to replace most of the MML research facilities during the term of its current 5-year strategic plan, the process for creating a long-range plan for facilities renewal for the MML, or even better, a NIST-wide plan, needs to begin promptly so that implementation toward a coherent whole can proceed in stages.

The CSD staff is approximately 20 percent of the MML staff; however, none of the MML NIST fellows or administrative staff are in the CSD. In total, 115 scientific staff members and approximately 50 associates in the CSD are supported by only 4 technicians and 8 support staff. This situation results in Ph.D. scientists doing most of the laboratory work that could be done by technicians, as well as most of the administrative tasks required for their research and development (R&D) work.

Additionally, there is substantial room for improving the efficiency and quality of the administrative support services for research. The procedures for purchasing supplies and equipment and for obtaining approvals continue to require too much time and effort on the part of the researcher and take too long for administrative action. The processes for requisitioning, approving, contracting, and completing maintenance repairs or alterations in buildings that are required for research function very poorly, if at all. In response to these perennial NIST problems and to the findings of the 2014 National Academies Assessment, the MML assigned some members of its technical staff to work 20 percent of the time on these processes affecting the CSD as well as other MML groups.

Some research institutions have made good progress for both the administrators and the researchers by keeping data on the accuracy, turnaround times, and costs for administrative processes. Such data are valuable for benchmarking the quality and cost of administrative work, for planning improvements, and for setting performance goals and standards in discussions with administrative staff. Tracking and sharing the data over time can build confidence in the groups and can enable both groups and individuals to be rewarded on the basis of quantitative standards.

The division has expressed concerns that access to costly pieces of equipment is limited to members of the group, or even just to the individual, that originally obtained it. Better access to equipment is achieved in many research institutions by establishing instrumentation centers, especially for commercially available instruments. Such centers include a technical staff member (or members) who educates and assists users, maintains upgrades, and ultimately replaces equipment. The economics of such service facilities depends on having enough of a variety of equipment and expert staff to satisfy the needs of the user base that fully utilizes such resources.

For some purposes, a group within the CSD has enough customers of its own. More often, the facilities will need to serve, and possibly be located, within other divisions or laboratories within NIST, or other research institutions within the greater Washington, D.C., metro area. Alternatively, the CSD may be able to satisfy some of its needs by purchasing time at existing facilities located elsewhere.

## **DISSEMINATION OF OUTPUTS**

### **Accomplishments**

The CSD's scientific staff members, NRC postdoctoral fellows, and graduate research associates produce many valuable types of outputs, each with its own unique variety of impacts. Specifically, the

CSD lists 335 journal articles (18 percent of the MML total) and 59 NIST reports (42 percent of the MML total) published since the 2014 National Academies Assessment (from April 1, 2014, to May 5, 2017).<sup>8</sup> This amounts to 1.96 journal papers per scientific staff member per year—or 2.3 including NIST reports. This is overall quite good considering that some scientific staff have duties, such as the creation and maintenance of SRMs, that rarely lead to publications.

The CSD is also responsible for the creation, documentation, production, and support of 60 percent of NIST's 1300 SRMs. This is a major contribution to industry and to all chemical scientists and engineers. The MML delivered 90,000 SRMs to customers during the last 3 years.<sup>9</sup> From May 2015 through March 2017 CSD staff responded to over 850 technical inquiries regarding the use of NIST SRMs that came from scientists in 62 nations and 46 states.<sup>10</sup>

The *NIST Chemistry WebBook* is an immense compendium of carefully documented and verified data on the properties of 80,000 chemical species used by more than 13,000 unique users per day. The NIST mass spectrometry database is incorporated into the software package for nearly every commercial mass spectrometer. The income from this product alone has averaged \$6.8 million per year for the past 3 years.

The Inorganic Crystal Structure Database (ICSD) is currently second in sales for the MML at \$0.65 million per year. The chemical reactions database makes it possible to calculate the rate at which products are formed in a chemical factory, in an automobile engine, or in the atmosphere.

Standard instruments, calibration samples, and methods are provided for by the CSD and include many types of spectroscopy used for basic research and applications; a data hub that supports the spectroscopic identification of novel psychoactive substances; RMs used to train dogs to detect explosives and illicit drugs by smell; the calibration of quantitative determinations in many types of hospital blood tests (including the latest metabolomics and gene sequencing techniques); and the measurement of the concentrations of noxious gases (carbon dioxide and other greenhouse gases) in the atmosphere of a city, or of ozone, in order to understand, predict, and protect humanity from lung disease, skin cancer, and global warming. Neutrons are being used to study the behavior of lithium ions in operating batteries, with potential major impact on the use of batteries on the national electric grid, in transportation systems, and with almost any electronic or electrical device.

The CSD's collection of marine specimens from the Marine Environmental Specimen Bank are collected, processed, and stored to provide valid historical comparisons for 50 to 100 years. These specimens will support building a detailed understanding of the evolution of ocean environments into the future and its impact on fisheries, coral reefs, and other ocean resources.

The CSD scientists also serve on 80 national and international standards committees and hold leadership positions on 6. They have many collaborations and information exchanges with other organizations, which constitute a substantial part of CSD's impactful output. The division works with the Centers for Disease Control (CDC), NOAA, the U.S. Navy, NASA, National Institutes of Health (NIH), the Arctic Monitoring and Assessment Programme (AMAP) of the Arctic Council, as well as with a wide range of industries. Continuing to expand these activities selectively will enhance NIST's impact.

## Opportunities and Challenges

To better enhance NIST's impact on the success of U.S. industry, the CSD can initiate personnel exchanges with key industries so that the CSD staff can have a deeper understanding of their needs. That would also enable industry personnel to learn of NIST measurement technologies, research methods, data sets, and other capabilities. This is one way that the CSD can apply its available research directly to industries' needs and to discuss additional ways in which NIST could be helpful. The CSD could also

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<sup>8</sup> NIST Material Measurement Laboratory, "Made to Measure," p. 156.

<sup>9</sup> *Ibid.*, p. 25.

<sup>10</sup> *Ibid.*, p. 148.

seek out start-up companies who are forging new directions that may require new standards and reference data. Additionally, it could serve on the committees of industry standards setting bodies. In doing so it could report on the acceptance and use of NIST standards in specific industries and on any needs for new standards.

The CSD could also adopt a collaborative approach with industry for setting goals and defining metrics for the value of NIST's work to industry and documenting the impact of NIST's work on industry. This could make a convincing case for funding to industrial leadership, to the DOC, and to Congress.

Additionally, it could take full advantage of the opportunities, industrial contacts, and resources available through the NIIMBL. They could both contribute to and monitor the programs and progress of the work at NIIMBL.

Finally, the CSD could ensure that early progress is reported as an editorial or as news in professional and industrial magazines and journals, in addition to the usual journal articles and NIST reports the CSD publishes in.

## Materials Measurement Science

### INTRODUCTION

The Materials Measurement Science Division (MMSD) is one of the largest divisions within the Material Measurement Laboratory (MML), with a total of 179 members: 99 National Institute of Standards and Technology (NIST) scientists, 5 technicians, 7 support staff, 3 fellows, and 65 NIST associates. Owing to the NIST and then the MML reorganizations in 2011, the MMSD was formed via the merger of three independent entities: the Ceramics Division from the Materials Science and Engineering Laboratory (MSEL); the Surface and Microanalysis Science Division (SMSD) from the Chemical Science and Technology Laboratory (CSTL); and a section of the Office of Law Enforcement Standards (now the Security Technologies Group). While most of the MMSD staff and facilities are in Gaithersburg, Maryland, the Synchrotron Science Group is located at the new National Synchrotron Light Source II (NSLS-II) facility at Brookhaven National Laboratory in Upton, New York. This group is responsible for the technical development, construction, and maintenance of three NIST beam line instrumental end stations. From a funding perspective, the MMSD is unique within the MML in that the division receives approximately 25 percent of its support from seven U.S. government agencies outside the Department of Commerce (DOC).

The MMSD conducts a mixture of priority-based fundamental research, standards production, and applied science that couples well with metrology efforts to address stakeholder needs. The MMSD maintains a very broad scientific portfolio encompassing five program areas: the Materials Genome Initiative (MGI); advanced materials; nanometrology; safety, security, and forensics; and synchrotron science. The strategic plan is to ensure that project goals and deliverables are clearly tied to NIST, MML, and stakeholder programmatic needs. Such goals are in place in order to provide managers the ability to analyze division and group portfolios to facilitate strategic and informed decision making. They also allow managers and staff to view competencies in a manner that permits the MMSD to become even more agile and effective in responding to NIST and MML priorities.

### ASSESSMENT OF TECHNICAL PROGRAMS

#### Accomplishments

The Microscopy and Microanalysis Research Group performs fundamental research, develops metrological methodologies, and disseminates results toward the compositional and morphological characterization of materials—from the mesoscale to the atomic scale—using electron, ion, and photon interactions with matter. Through detailed measurements, comprehensive analysis and modeling,<sup>1</sup>

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<sup>1</sup> NIST, Microscopy and Microanalysis Research Group, <https://www.nist.gov/mml/materials-measurement-science-division/microscopy-and-microanalysis-research-group>, accessed September 25, 2017.



theoretical methods, and multidisciplinary microscopy, this group advances and promotes microanalysis to address stakeholder needs in diverse arenas of materials science.

The Nano Materials Research Group develops innovative metrology to advance nanomaterial research and applications for the benefit of U.S. commerce. Best-in-the-world measurement science is both developed and used to determine the physical and chemical properties of a wide variety of organic, inorganic, biomolecular, and hybrid systems, where materials of interest fall within the nanoscale regime.<sup>2</sup> The resulting standards, methods, reference methods (RMs), and measurement data advance a wide range of technologies and stimulate innovation.

The Materials for Energy and Sustainable Development Group conducts research and develops and disseminates measurement science, data, standards, and technology that pertain to energy-related materials, and materials for sustainable development. Using the MGI approach, the group explores and evaluates the efficient use of materials in manufacturing, transportation, infrastructure, and water. Its activities encompass materials efficiency (conservation, use of earth-abundant elements, substitution, reusing, repurposing, recycling, and lightweighting), materials life cycle assessment, critical materials, materials flow analysis, and mitigation of undesirable impacts on the environment and on human health.

The Surface and Trace Chemical Analysis Group develops, improves, and standardizes analytical techniques used for the elemental, organic, isotopic, radiological, and morphological characterization of surfaces, thin films, and particles. It also develops novel methods of chemical analysis based on optical microscopy, mass spectrometry, chromatography, ion mobility spectrometry, spectroscopy, autoradiography, nuclear counting, and nuclear track methods.<sup>3</sup> It also conducts research in generation and size calibration of particle standards. Additionally, the group researches fundamental aspects of the trace detection of explosive and narcotic particles (including the use of computational fluid dynamics and advanced flow visualization). It also develops standard test materials by application of advanced inkjet dispensing technologies, and it applies multiple surface, trace chemical, and nuclear analysis methods to problems in forensics, additive manufacturing, materials science, semiconductor technology, bioscience, and homeland security.

The Synchrotron Science Group develops and disseminates measurement science and technology pertaining to the measurement of the structure, including chemical and electronic, of advanced materials by synchrotron methods. The group provides, maintains, and supports synchrotron measurement capabilities as part of the DOE User Facility Program,<sup>4</sup> which is primarily located at the NSLS-II.

The Materials Structure and Data Group develops and disseminates measurement science, standards, and technology for determination of the structure of advanced materials. The group determines, compiles, evaluates, and disseminates key data and computational tools (such as those for the prediction/interpretation of spectroscopy data) needed to establish the relationships between the structure and performance of inorganic and hybrid materials and devices.<sup>5</sup>

The Nanomechanical Properties Group develops and disseminates measurement science, standards, and technology pertaining to the measurement of mechanical properties of advanced materials and structures at the nanoscale. The group determines, compiles, evaluates, and disseminates key data needed to establish the relationships between structure, mechanical properties, and the performance of inorganic and hybrid materials and devices.

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<sup>2</sup> NIST, Nano Materials Research Group, <https://www.nist.gov/mml/materials-measurement-science-division/nano-materials-research-group>, accessed September 25, 2017.

<sup>3</sup> NIST, Surface and Trace Chemical Analysis Group, <https://www.nist.gov/mml/materials-measurement-science-division/surface-and-trace-chemical-analysis-group>, accessed September 25, 2017.

<sup>4</sup> NIST, Synchrotron Science Group, <https://www.nist.gov/mml/materials-measurement-science-division/synchrotron-science-group>, accessed September 25, 2017.

<sup>5</sup> NIST, Materials Structure and Data Group, <https://www.nist.gov/mml/materials-measurement-science-division/materials-structure-and-data-group>, accessed September 25, 2017.

The Securities Technology Group conducts research and develops and disseminates the measurement science to support the development of performance-based standards and to promote the advancement of their technologies. Such technologies are used in trauma-mitigating materials and material systems; the sensing of concealed threats and contraband; advanced composites; high-performance materials; and safety, security, and forensics.

### **Opportunities and Challenges**

The technical programs within the MMSD are excellent and there are many talented staff members and enthusiastic postdoctoral researchers. It is clear there is a strong culture around the NIST mission with a strong commitment to technology and knowledge transfer. The staff clearly understands that it is uniquely positioned to satisfy national needs, and it works effectively with industry. It is clear there is a willingness to engage with customers, as illustrated by its diverse set of partners and collaborators. It is unclear, however, what the core strategy of the division is and how the different groups fit into the division. How are future program trajectories determined, and how does that align with where the division sees itself in 1, 5, or 10 years?

There seems to be uneven awareness of overlapping expertise and equipment across the groups and divisions. Also, being spread over eight buildings creates some barriers to natural interactions. The MMSD leadership will need to break down silos and create opportunities and incentives for the staff to connect. There are current grass-roots efforts to keep connected by having teas, seminars, and picnics, but it is not clear how well this is working.

It is questionable how the MMSD focus on ballistics work fits into the core NIST mission. The MMSD needs to make sure there is a good connection between the Security Technologies Group and the division. It also needs to connect the ballistic body armor work to similar work at Department of Energy (DOE) and the Department of Defense (DOD) laboratories. Similarly, there is work in trace chemical detection and sensors at other DOE laboratories, and it is unclear whether it is leveraging or communicating with those other efforts.

As an organization, the MMSD is recognized and valued, nationally and internationally, for its technical excellence. Building core competencies at this high-performance level is, by nature, often a career-long endeavor. Yet, as the *pace of change* in scientific discoveries and technological advancements accelerates, the ability to quickly respond to new materials science problems is increasingly important to MMSD's stakeholders. The rapid response challenge is twofold: the ability to quickly adapt existing measurement competencies to meet new needs, and the timely development or acquisition of new competencies to address novel measurement science problems. Such challenges exist at both the programmatic and business-of-NIST (procurement) levels.

Program leaders within the MMSD are faced with an ever-increasing need to rapidly assess stakeholder needs, prioritize these needs, assemble (and acquire, if necessary) the required expertise, and develop and complete new programs and projects. Developing the necessary agility to deliver to customers and stakeholders without compromising excellence will require NIST to adopt a new operational culture that integrates a focus on rapid response to stakeholder needs, recruiting the required expertise, and developing new programs.

The MMSD needs to ensure that it not only maintains the high levels of expertise expected of a national metrology institute but also can deploy necessary competencies quickly and effectively. Balancing the need for a long-term research program to maintain excellence in core competencies that serve the existing customer base with the ability to be responsive to new customers' needs is a challenge.

## PORTFOLIO OF SCIENTIFIC EXPERTISE

### Accomplishments

The MMSD staff consists of 99 NIST scientists, 5 technicians, 7 support staff, 3 fellows, and 65 NIST associates. The staff members are scientific leaders in the areas of X-ray methods, electron microscopy, and surface analysis. Materials measurement science in the MMSD is applied at multiple time and length scales, and spans a diverse range of scientific expertise.

The Synchrotron Science Group at the Brookhaven NSLS-II is noteworthy for its leadership and innovation in synchrotron spectroscopy and imaging methods, particularly in the regime of soft X-rays. The successful execution of its long-range plan to develop cutting-edge and, in some cases, one-of-a-kind end stations is to be commended. The investments and developments there are enabling cutting-edge methods that will provide new capabilities in measurement science.

The expertise in the Materials Structure and Data Group is strong in local structure and subnanoscale measurements, including point defects and complex real-world structures. For complex, real-world structures, the group develops first-principles-based methods for prediction of atomic arrangements and properties and also studies advanced ceramics and inorganic materials, which are critically enabling elements in real-world devices and complex systems across many technology sectors, such as telecommunications and energy. Collaborations with external industry partners appear to be fruitful and are strengthening the impact of the groups. The expertise in crystallographic and phase equilibria databases remains among the best in the world and exemplifies a key role that NIST plays in supporting industry and the larger scientific community.

In the Microcopy and Microanalysis Research Group, the expertise in metrology and compositional and morphological characterization of materials is creating advances with tangible impact to measurement science. Advances in measurement science instrumentation for atom probe and multimodal microscopy are highlights of this group's expertise.

The Surface and Trace Chemical Analysis Group shows NIST's role in both measurement science and real world impact. The group has the expertise to push measurement science for trace chemicals and surface analysis with tangible connection to detection needs for security and forensics.

The Materials for Energy and Sustainment Group has expertise in energy-related materials; materials for sustainable development; the efficient use of materials in manufacturing, transportation, infrastructure and water and material efficiency (conservation, use of earth-abundant elements, substitution, reusing, repurposing, recycling, and lightweighting); materials life cycle assessment; and mitigation of undesirable impacts on the environment and human health.

The Nanomechanical Properties Group has developed special expertise in the technology pertaining to the measurement of mechanical properties of advanced materials and structures at the nanoscale. The group has the ability to determine, compile, evaluate, and disseminate key data needed to establish the relationships between structure, mechanical properties, and performance of inorganic and hybrid materials and devices.

The Security Technologies Group has expertise in the development of performance-based standards and the advancement of the technologies used in trauma-mitigating materials (such as those used in helmets to decrease the incidence of traumatic brain injuries) and material systems and the sensing of concealed threats and contraband.

The Nano Materials Research Group has established expertise in nanoparticle separation and analysis. The nanometrology of particles for development of NIST standards is well aligned with NIST's mission. The applied research in this group is good, and the structure and chemical characterization expertise is excellent. It is encouraging to see the integration of the scientific staff with the broader community in areas that are too big for one group or institution to tackle.

From speaking with the MMSD postdoctoral fellows and early career staff, it is exciting to see the level of diversity both in breadth of expertise as well as with regards to representation from underrepresented groups.

## Opportunities and Challenges

While the MMSD work on nanoparticle separation and high-throughput analysis is very good (it includes measurements and standards for scanning probe microscopy, nanoscale strength, and nanoscale stress), it is not evident that the MMSD nanoparticle expertise is equally strong in all areas of this broad and rapidly expanding field. What innovations are being considered in anticipation of the near-future needs is also not evident. The Materials and Structure Data Group might benefit from increased collaboration with the Synchrotron Science Group at Brookhaven.

The through-barrier radar systems (a pulse-Doppler system using a narrow-band swept-frequency source operating between about 500 MHz and 3.2 GHz, which supports measurement science test methods, test artifacts, and data analysis) are becoming available and the work being performed by the MMSD to develop standards for their performance is extremely timely and important.

The competency database is a good idea for identifying scientific expertise; however, there is a risk in relying on individual input to populate it. The MMSD needs to leverage other databases from which key words could be extracted, such as from publications and presentations.

The junior staff is excellent and reflects the success of the National Research Council (NRC) Associateship Program to attract energetic researchers to the division. They appear very happy with the research environment and are well mentored by the senior staff. Most would like to stay in a permanent position, but they have expressed concern about the increasing demands of paperwork and restrictions on travel.

Because of the dearth of technicians, it appears Ph.D. scientists do routine tasks like equipment maintenance, which is a poor use of their skills and resources and limits productivity. There is a strong need for technician support also in the area of information technology (IT), particularly in view of the mandate to make all data public. More technicians would make the staff more efficient. The postdoctoral fellows are not meant to be primary equipment maintainers.

Long-term process improvements and sound decision making will be required. Additionally, the MMSD needs to leverage other laboratories (the DOE Office of Science and the National Nuclear Security Administration [NNSA], in particular) and universities (the University of Michigan, Stanford University, etc.). There needs to be transparency of how to succeed, especially for early career staff. The MMSD needs to leverage NIST's postdoctoral network with a professional development program in order to improve connectivity across NIST.

While the staff is excellent, it receives few external awards and has little professional society engagement. External awards for NIST staff bring visibility to the caliber of work and the contribution of NIST to the scientific community. While the MMSD personnel win some external awards, they do not win the number they deserve for the quality of the people and the quality of the work that they do. External awards won by the MMSD include the following: the IEC's 1906 award, the Roon Foundation award, Fellow of the ACS, Fellow of the Royal Society of Chemistry, ASTM Committee F12 Award of Excellence, the International Centre for Diffraction Data (ICDD) Distinguished Fellow Award, American Ceramic Society (ACS) Robert B. Sosman Award and Lecture, and the ACS James I. Mueller Award and Lecture. Of these awards only two—the ASTM Committee F12 Award of Excellence and the ICDD Distinguished Fellow Award—were won in 2017; the rest were won in 2014. With more organized internal effort, more personnel could become fellows and award winners of the professional societies. There needs to be more of a push for external awards, and involvement in professional societies needs to be more encouraged.

## ADEQUACY OF FACILITIES, EQUIPMENT, AND HUMAN RESOURCES

### Accomplishments

Overall, the quality and quantity of the equipment at the MMSD is excellent, consistent with the MMSD mission to pursue state-of-the-art metrology, microscopy, and spectroscopy. Within the division, there are a number of capabilities to measure and characterize materials that are unique, either to NIST or to the broader international research community.

The Safety, Security, and Forensics program within the MMSD strives to provide the underpinning measurement science needed to advance threat detection, improve the accuracy of forensics measurements, and ensure the reliability of protective technologies and materials in ways that enable homeland security, the safety of public servants, and effective law enforcement. Chemical microscopy and particle characterization techniques have been developed in the MMSD to evaluate the threat signatures associated with trace explosives detection. A database of the attributes and morphologies of particles in fingerprints and other residues associated with the handling of explosive powders and formulations has been assembled, thereby setting realistic criteria for materials used in technology development and testing. The MMSD has developed several new ambient ionization mass spectrometry techniques that allow, for the first time, chemical analysis of both inorganic and organic explosive and narcotic compounds on surfaces. This development expands the analysis of contraband materials to the analytically challenging but critically important area of homemade explosive formulations—which are difficult to detect with currently deployed technology.

The MMSD maintains two through-barrier sensing and imaging capabilities: (1) a narrow-band doppler-radar-based system ( $\approx 3.6$  GHz) that can sense humans located inside buildings, buried in rubble, or obscured by foliage, thereby targeting applications in law enforcement and emergency response; and (2) a broadband ( $\approx 200$  MHz to 5 GHz) holographic imaging system, with a large aperture size ( $\approx 20$  m  $\times$  4.5 m) to provide large-area images of objects behind walls. In addition, the MMSD, in collaboration with the Physical Measurement Laboratory (PML), has developed a state-of-the-art video-rate passive submillimeter-wave imager for detecting threats concealed on a person up to 20 miles away. This imager holds great promise for standoff threat detection. Further, a testbed is maintained for evaluating the imaging performance of the portable X-ray systems used by domestic and military bomb squads, the ubiquitous carry-on baggage X-ray inspection systems, and the backscatter and transmission X-ray systems for body screening. These provide the basis for the development of test artifacts, objective and automated image analysis routines, and international documentary performance standards.

The main objective of the Nanometrology program is to develop or create new measurement techniques and applicable standards to meet the needs of various stakeholders that rely on high-quality nanometer-scale material characterization and associated technologies.

A key measurement capability for advanced materials involves the use of contact resonance atomic force microscopy (AFM) to measure the mechanical properties (elastic modulus) of surfaces at the nanoscale. Recent MMSD efforts have focused on refining models, calibration, and standards—extending the range of applicability to a wider range of harder materials. It has also focused on the development of a new technique—intermittent contact resonance atomic force microscopy—to provide additional depth-sensing capability on nanostructured materials.

The Surface and Trace Chemical Analysis Group has an excellent set of commercially based instruments, including secondary ion imaging and tomographic atom probe analysis coupled with laser excitation of surface atoms.

NIST and the DOE have had a 35-year ongoing partnership at the National Synchrotron Light Source (now NSLS-II) developing advanced synchrotron measurement methods and delivering excellence in material science. NIST is currently constructing an NSLS-II spectroscopy suite of three state-of-the-art high-throughput beam lines (with X-ray diffraction capability); soft and tender X-ray spectroscopy and microscopy (100 eV to 7.5 keV) and hard X-ray absorption spectroscopy and diffraction (4.5 keV to 22 keV). The suite is expected to be completed in 2017. The NIST NSLS-II Spectroscopy Beamline Suite

will be able to measure the electronic, chemical, and structural properties of almost any material, often at the nanoscale. This facility will provide unique opportunities for collaborative research within the MMSD, with MML personnel across divisions (including the Boulder, Colorado, facility), and with the broader user community—including numerous industrial partners.

### **Opportunities and Challenges**

Across the MMSD, the majority of facilities were in excellent condition. In contrast with some other divisions, the MMSD has facilities that largely match the needs of its staff and instruments. One challenge is that facilities are distributed across eight buildings, which can require more effort to make the groups aware of each other's capabilities. Also, for new capabilities that are at another site (such as at NSLS-II), it will be important to raise awareness across the MML of new capabilities that could be leveraged by other groups.

During the past three years, NIST has made large investments in two important MMSD-led research facilities that were developed in partnership with the DOE. These facilities are the NIST NSLS-II beam lines, which are located at Brookhaven National Laboratory and the Facility for Adsorbent Characterization and Testing (FACT) laboratory, which was developed by funding from the DOE's Advanced Research Projects Agency-Energy (ARPA-E) and is located at the NIST campus in Gaithersburg, Maryland. NIST's NSLS-I beam line suite of instruments has been very successful in accelerating the development of new materials into devices and systems with advanced capabilities. The NIST's NSLS-I user community has averaged about 100 users per year. Building on this success, the goal for the new NSLS-II is to grow that community as new instruments come on line later in FY 2017. DOE infrastructure is in place to support the process of hosting users, and the MML Laboratory Office has provided support to increase internal and external outreach efforts. The MMSD will maximize the use of this facility by NIST staff and associates, and has been reaching out to additional external users. The challenge for both facilities involves growing the user community with existing staff resources (i.e., without devoting additional resources). If successful, this will provide the opportunity to further extend the MMSD outreach into the materials science community.

The scientific instrumentation is generally of extraordinary quality across many of the groups. Some pieces of equipment are unique, with cutting-edge capabilities, and some are among the best in the world, matching the quality of the staff. There is a lot of high-end capital equipment, and there are questions about how to maintain that investment and maintain or upgrade the facilities infrastructure. For example, how does the MMSD decide what to invest in next, what to replace, and what to let go of? One of the challenges here will be continued investment in maintaining and replacing key instruments.

The human resources are highly accomplished, collaborative, and effective in their equipment usage. The MMSD has been very successful with recruiting diverse, early career scientists, but there are some concerns around intentional fostering for retention. A challenge for the MMSD will be in how to invest in staff members to position them for professional growth and to nurture their retention at NIST. Exemplifying careers that bridge fundamental science up to tech transfer is a good idea. Additionally, the MMSD could use workshops to help raise knowledge of all staff. Having a stable workforce is positive, but it also makes it more difficult for staff promotions. Additionally, the MMSD needs to improve succession planning.

## **DISSEMINATION OF OUTPUTS**

### **Accomplishments**

During the last 3 years, the MMSD personnel have published 467 papers in archived journals, 44 conference proceedings, 21 NIST reports, and 18 books and book chapters. The division's publications

are in a broad range of fields, reflecting its diverse research activities, and over the past year, have included publications in high-impact journals such as *Nature Materials*, *Nano Letters*, *ACS Nano*, *Advanced Energy Materials*, *Advanced Functional Materials*, *Chemistry of Materials*, and *Small*. Many of the papers are coauthored with researchers outside of NIST—an indicator of successful collaborations.

Patenting is secondary to many other success metrics for almost all MMSD staff researchers, and during the last 3 years there was only 1 patent issued, 1 published, and 3 more filed.

The MMSD works closely with industrial partners. During the last 3 years, it has held 21 workshops, including one workshop on the *Qualification of Uncertainties in Material Sciences*, another one on *Measurement Needs in Adsorption Sciences*, and a third workshop on a focused ion beam scanning electron microscope (FIB SEM). There have been one Cooperative Research and Development Agreement (CRADA) and 42 interagency agreements with seven different agencies.

The division has developed three commercial swipe technologies, and three printer systems have been commercialized. It sells approximately 1700 RM units per year, of which there are almost 80 different types. These materials cover a variety of needs, including X-ray diffraction characterization and calibration, particle size (including nanoparticle sizing), glass viscosity, refractive index, surface area, and chemical composition. About 20 percent of the customers are from academia; 20 percent from state, local, and federal governments; and 60 percent from industry.

Examples of new MMSD products include SI-traceable standard reference materials (SRMs) for calibration of varying diffraction measurement methods. This product is highly effective, and there is hardly an X-ray diffractometer in the world that does not use the NIST standard—roughly a third of new instruments sold worldwide include a NIST standards diffraction package.

The MMSD also provides SRDs covering crystallographic and structural information, phase diagrams, surface spectroscopy, ceramic properties, and X-ray and image analysis, all of which are used worldwide. These standards are a major resource for researchers, and the MMSD expends enormous efforts to incorporate image processing and theoretical/statistical methods within materials databases to expedite experimental data standardization and evaluation.

The MMSD representation on standards-setting committees is outstanding and is a significant output of the division. Many MMSD staff members actively participate on committees in 130 international standards organizations (primarily American Society for Testing and Materials [ASTM] and International Organization for Standardization [ISO]). This participation includes standards committee leadership. Noteworthy examples of standards activities include the following:

1. Absolute Intensity Calibration Standard for Small-angle X-ray Scattering (SAXS; SRM 3600). SAXS measurements characterize the microstructure and nanostructure of heterogeneous material systems—specifically, size distributions of microscale and nanoscale features, volume fractions or number concentrations, and surface areas.
2. The Securities and Technology Group led a significant revision of the internationally used documentary performance standard for cabinet X-ray systems used for carry-on baggage at airports and other security checkpoints.
3. The suite of six X-ray diffraction (XRD) SRM's provide SI-traceability for calibration of all diffraction measurement methods. All of the manufacturers of the XRD instruments worldwide include a NIST diffraction SRM(s) as the calibration standard.
4. The Fachinformationszentrum Karlsruhe (FIZ)/NIST Inorganic Crystal Structure Database (ICSD; SRD 84) is a collection of crystal structure data for nonorganic compounds including inorganics, ceramics, minerals, pure elements, metals, and intermetallics.
5. The MMSD initiated a collaborative effort with the Food and Drug Administration (FDA) and industry members to develop a new standard test method for size measurement using dynamic light scattering.

Finally, the MMSD has generated for other agencies significant outputs that, for security reasons, are not included in its list of publically available publications.

## Opportunities and Challenges

Across the MMSD, the internal assessment of output seems satisfactory and recognizes the different expectations placed on different individuals. Communicating tailored expectations of output based on the role and projects of each staff member needs to be continued. Staff members need to feel empowered knowing the output requirements of each activity they undertake—whether it is authoring a publication, developing an SRM, or developing a new instrument or technique. Staff members need to feel secure knowing that those outputs will be valued in merit reviews and decisions, and ongoing efforts to communicate the various paths to success at NIST need to be continued.

The MMSD has a solid publication rate. For future National Academies laboratory reviews, it would be good to see the author list separated by visiting faculty versus staff to see what is NIST-driven and what is external collaborator-driven. While both first authorship and coauthorship of publications appear to be valued, it seemed that the former was regarded as having higher value. In characterization work, it can be that the paper was largely enabled by the contributions of one author, regardless of final author order. And so, discerning value of the author's contribution to the paper could enable staff members to directly articulate the impact of their work.

One other aspect of output is the rigor of the data collected. The MMSD largely excels in this area, applying statistical analysis to optimize the quality of data and conclusions. One challenge here though is in the consistency of applying experimental design and statistical analysis across all groups. The uniform application of experimental design (when the project is conducive to it) and statistical analysis is needed. Particularly for exploratory work, making the design of experiments more uniform (when the project is conducive to it) would improve efficiency in determining salient variables to explore. Additionally, the MMSD needs to reach out to other parts of NIST to access statistical expertise that already exists.

Many workshops have been held at NIST, and this is highly beneficial for dissemination of information. Connection to the Office of Data and Informatics (ODI) needs to be encouraged to leverage what the MMSD is developing. More consistency is also needed in the design of experiments. Particularly for exploratory work, the uniform application of experimental design (when the project is conducive to it) would improve efficiency in determining salient variables to explore.



## **Materials Science and Engineering**

### **INTRODUCTION**

Within the Materials Science and Engineering Division (MSED), there are a total of 194 staff members, which includes permanent staff, postdoctoral fellows, associates, and administrative support. In 2014, the staff was 182, and so the total staff count has grown by 12 over the past 3 years. The MSED staff represents about 19 percent of the total MML staff. The budget for 2017 is \$27.3 million, and this includes indirect costs.

The MSED covers a broad range of activities in five research areas: additive manufacturing, dynamic measurements for materials manufacturing, the Materials Genome Initiative (MGI), the foundry for functional materials measurement, and infrastructure renewal. The MSED made six presentations during the review, which focused on the Polymer Processing Group, the Thermodynamics and Kinetics Group, the Mechanical Performance Group, the Polymer and Complex Fluids Group, the Functional Polymers Group, and the Functional Nanostructured Materials Group.

### **ASSESSMENT OF TECHNICAL PROGRAMS**

#### **Accomplishments**

The Thermodynamics and Kinetics Group consists of 12 permanent staff and 11 research associates. The group is to be commended for its excellent progress since the last review. It is highly competent and working well together. Its engagement in the Center for Hierarchical Materials Design (CHiMaD) program with Northwestern University and the University of Chicago appears to be very strong. The group has made many computational tools and software available to a diverse range of users. The group is involved in computational materials science from the atomistic level to the continuum level—often bridging scales. Its ability to bridge scales is important because it enables the group to compare theoretical predictions with experimental results. The quality of computational materials science, particularly in Computer Coupling of Phase Diagrams and Thermochemistry (CALPHAD), density functional theory (DFT), multicomponent diffusion, atomistics, and phase field, are among the best in the world in computational modeling and alloy development in metals. These tools are branching out into, and complementing, computational tools in soft materials. An example of this core competency is validated by the National Institute of Standards and Technology (NIST) leadership role in the MGI, where for example, the objective of the Thermodynamics and Kinetics Group is to develop materials informatics and computation tools to advance the initiative, with accomplishments such as the Customized DSpace, Interatomic Potential Repository, JARVIS-FF, and JARVIC-DFT to name a few. The materials design toolkit is providing value for the entire computational materials community.

The group is also studying some very complex problems such as multicomponent alloys systems. It is predicting properties and experimentally verifying them. An example is the Al-Co-W system. The prediction of the diffusion coefficient and its verification by experiments is an important accomplishment.

Also, its studies on changes in material structure after thermal treatment following additive manufacturing of IN625 alloy is a good accomplishment. Design of Cu-Ni-Zn alloy as a replacement for nickel (requested by the U.S. Mint) is an excellent example of materials design and experimental demonstration. This switch to an alloy is expected to significantly lower the cost of a nickel.

The Mechanical Performance Group demonstrates best-in-the-world work on highly quantified mechanical performance in multiaxial stress state applications. The cruciform tester has high industrial relevance for fabrication and end product reliability and safety. It would be good to evaluate the mechanical performance capability at the NIST Boulder, Colorado, facility for a complete perspective of testing capability. One indicator of best-in-the-world human resource expertise is that the group has been asked to give its consultation on national-level failure analysis issues such as the World Trade Center collapse.

Automotive lightweighting is highly important to our nations' energy use profile and global CO<sub>2</sub> reduction goals. The cruciform testing work being performed at the MSED directly impacts the lightweighting of automotive body closure sheet. An example is Ford's F-150 lightweighting efforts as well as General Motors's (GM's) steel lightweighting efforts. There were strong signs of the group's industrial engagement as evidenced by interaction with Ford Motor Company on C-fiber and GM on ultra-high-strength steel sheet for transportation lightweighting. There was also clear evidence of an open source focus of tools, such as Python, which aids adoption by the technical community. Two notable, innovative projects that are drawing closer to completion are coinage (patents pending) and co-based super alloy development, which is essential to jet engine fuel efficiency.

Collaboration with six other organizations on additive manufacturing, with respect to the role of accurate measurements in this highly active field, demonstrates the philosophy of providing value and not just researching in a *hot* field. This is a clear niche where NIST brings value to the additive manufacturing community. The NIST-founded Additive Manufacturing Benchmark Test Series (AM Bench) and its depth of expertise in physical metallurgy are other areas that differentiate NIST from other laboratories in additive manufacturing.

Substantial leadership on the American Society for Testing and Materials (ASTM) and other standards committees is viewed by industrial reviewers as highly advantageous. NIST staff members are unbiased and provide sound perspectives, particularly when committees are composed of other members, such as suppliers and users of materials that can financially benefit from specific wording within specifications.

The Functional Nanostructured Materials Group is to be commended for its excellent progress. Extreme bottom-up superfilling is a high-visibility contribution, which has been carried out over more than a decade. It is used by industry to guide the development of advanced superfilling systems of different geometry and materials, and offers an opportunity to focus more on scientific mechanisms. Self-termination electrodeposition used to deposit mixed-metal thin catalytic films with superior catalytic properties is another example of a notable achievement.

The group is conducting work on electrochemical microscopy, which is an established method. However, the group is using it in a novel way. Still, it would be useful to highlight how this differs from traditional electrochemical microscopy. In situ stress measurements such as short-term and long-term stable methods are valuable. Linking to wider applications would require collaborative interactions to build on NIST's fundamental scientific accomplishments.

The group's research on the electrocatalysis of formic acid oxidation to produce CO<sub>2</sub> formation without CO poisoning is an advance that builds on in situ experiment and theory. The group also maintains a close connection between modeling and surface analysis. The transmission electron microscopy (TEM) tracking of the Li-ion battery and moving to DYNAMIC observations are good examples of its other accomplishments.

Accomplishments within the Polymer Processing Group, the Polymers and Complex Fluids Group, and the Functional Polymers Group are discussed later. These include the synthesis of near-perfect short branch spacing polyethylenes (which may become the basis for some new and needed polyolefin standard reference materials [SRMs]) and the synthesis of model networks using cyclic polymers that produce

cross-linked networks with no dangling ends. Other examples of significant accomplishments include the control of surface exchange between a surfactant and DNA; the NIST on a chip initiative using holography in collaboration with CHiMaD; the development of the ZENO tools for the calculation of several polymer properties (some aspects have very recently become publicly available); a new approach to coarse graining of polymer dynamics, the use of quasi-elastic neutron scattering to quantify electrolyte dynamics in solid polymer electrolytes; and the use of fluorescence probes to locate water invasion into composite materials.

Four projects within the MSED—the additive manufacturing of metals, mechanical standards, performance under extreme conditions, and automotive lightweighting—are highly pertinent to achieving national goals throughout the materials innovation continuum. The MSED’s leadership in the digital image correlation for strain measurement is also establishing needed best practices worldwide. The scientific expertise necessary to achieve technical goals and make major advances is excellent. Additionally, computational modeling and characterization of materials within the MSED is clearly among the best in the world, and there is substantial value in both validating and balancing computational modeling with experiments. NIST could foreseeably reestablish its role as the leader among government agencies.

The strategic planning process as well as the first strategic plan are viewed as a positive experience by the MSED. There are additional questions concerning the level of individual and group training in the tactical implementation of plans, as well as the facilitation of this process. It appears, however, that the group is now learning how to best develop and implement tactical plans that flow from the strategic plan. Strategic and tactical planning takes years to internalize into an organization and this is a positive start.

The researchers within the MSED also articulated that bringing technical value and being wise about spending taxpayer dollars is a key concept that drives many of their program (and equipment) decisions. These decisions include crosscutting collaboration between groups and other branches of government; scientific and technical recognition; a learning environment; an angel investing program; science, technology, engineering, and mathematics (STEM) participation with local high schools and community colleges; and alternative career path options; among others.

## **Opportunities and Challenges**

Opportunities to improve technical programs within the MSED include conducting more experimental work in conjunction with modeling to verify predictions across a number of systems. This may be better achieved by using model systems, which are easier to model with computational methods, and also may be easier to fabricate experimentally. The current focus seems to be on rather complex systems. The complex nature of these materials may make it difficult to truly design materials from the ground up, especially when the processing conditions are far from thermodynamic equilibrium. Under such circumstances, researchers may need to use multiple fitting parameters to compare with the experimental results. If the actual processing is under conditions far from thermodynamic equilibrium, the use of kinetic and transport parameters would be needed to achieve congruence between theory and experiments.

The work on magnetic nanoparticles is excellent. There is a potential opportunity to apply this research in the field of medicine. The group may want to consider linking to medical community users and researchers, both within and outside of NIST.

There is worldwide activity in magnetic materials, energy storage, nanowires, and Li-ion research. Given the limited manpower and resources, it would be useful to reevaluate where the MSED can make unique contributions to such activities to ensure that it is not spreading itself too thin.

The modeling capabilities within the MSED are good. One opportunity could be to make modeling superfill codes reusable by others, so that they could both be useful to investigate different mechanisms, and to compare with modeling. Additionally, the field of electrochemistry has an enormous physical

property database that could be utilized by NIST. For example, there is a property database on molten salts.

There is also an opportunity to work with the MGI to participate in the discovery of new electrocatalysts and other materials with potentially unique properties.

Also, given the limited manpower and resources, it would be useful to reevaluate the balance between long-term goals and short-term projects approaching maturity.

Routine methods are available for tracking error bars in experimental and computational studies. Their use is encouraged for uncertainty quantification when data and numerical results are combined in composing predictions for more complex systems. Tracking error sources and modeling uncertainty can assist in helping researchers decide where to invest their energies, in order to make improvements (i.e., more experimental data, improved assumptions, empirical corrections that reduce methodological errors, or better management of basis set truncation errors) in a complex system.

While there is considerable expertise in electrochemistry and engineering processing at NIST, it seems to be dispersed among other programs. Synergies might be possible for building new research directions. Examples include the pH measurements conducted and collaboration with the Marine Biochemical Sciences Group. Other examples include exploring the use of solid electrolytes in chemical science for nuclear chemistry. Collaborations can be envisioned with the Functional Polymers Group for work on various transport membranes.

New initiatives from *bottom-up* ideas can help to maintain a dynamic balance as *top-down* projects mature. Small projects can help to sustain technical programs, as their objectives are achieved, and new directions present themselves.

Finally, in future reviews, the use of poster sessions would provide direct contact between staff and reviewers. Such activities are useful for assessing the depth of expertise brought to bear on projects, and also for assessing the knowledge of whom else in the field, past and present, is highly regarded.

## PORTFOLIO OF SCIENTIFIC EXPERTISE

### Accomplishments

There is a very good mix of theorists and experimentalists within the MSED. Many of the scientific staff and postdoctoral fellows have strong backgrounds in fundamental sciences and engineering. Several have degrees in physics, applied physics, chemical engineering, and materials science and engineering. Postdoctoral fellows and staff have opportunities to attend professional meetings, present their work, and gain exposure to the work of other researchers. This also helps them to grow professionally, as well as make changes in their career paths—for example, some have recently joined academia.

Many MSED researchers have excellent citations to their published work, which shows that their work is recognized by the scientific community at large. It was noted that there are at least five researchers with over 4000 citations. Many have received prestigious NIST internal awards (bronze and silver medals).

One example of organizational expertise concerning human resource issues was the hiring of bachelor of science-level and master of science-level engineers into technician roles to improve productivity. This close partnering of senior researchers with technicians has been very fruitful for improving testing throughput and improving the quality of the output of the tests themselves in a very cost effective manner. This organizational model may have utility in other groups.

There has been an expansion from a pure science focus toward an engineering focus that provides additional short-term and long-term value for the United States. It is important to note that the quality of pure science did not suffer from this expansion of focus into engineering, which is a testament to the collective openness of the members of the MSED. There exists a positive employee culture within the MSED. There are many components to job satisfaction, and there is extensive management thought and action given to nonfinancial factors that impact job satisfaction.

## **Opportunities and Challenges**

The scientific staff within the MSED is first rate. Many have received internal awards and recognitions. It is important that the MSED management put a structure in place that will, on a regular basis, nominate scientific staff for external awards—such as awards from professional societies. Many societies have junior-level awards, and several also have high-profile external awards (e.g., the American Physical Society [APS] Fellowship; the American Chemical Society [ACS] Fellowship; The Minerals, Metals, and Materials Society [TMS] William Home-Rothery Award and Brimacombe Medal; and the American Society of Materials [ASM] Gibbs Award). Enacting such a structure needs to be made a priority.

One of the challenges is how to utilize postdoctoral fellows more effectively in ways that will help both them and also the institute. There was a concern that postdoctoral fellows have to spend a lot of time learning equipment maintenance and troubleshooting. They are not experienced in this, and are typically only in their positions for a couple of years. This can potentially lead to inefficient use of the postdoctoral fellows, and may also impede their progress toward career goals in research. It may be better to hire some engineer-level permanent staff to maintain the equipment. This may actually lead to increased research productivity, which is already very good. Additionally, staffing for the facilities would benefit from training, technical maintenance, and modernization.

There is high reliance on postdoctoral candidates for succession planning of top-level researchers. And so, succession planning opportunities exist within the MSED.

Linking with the Boulder Statistics Group may be beneficial, since that group reviews the literature, and evaluates and sells data. It also scans publications to assess the quality of the data and stores this data. NIST's Joint Army Navy Airforce (JANAF) Thermochemical Tables are valuable collective data compilations. Last, the MSED also needs to look across other programs to develop a collaborative effort and utilize available expertise.

## **ADEQUACY OF FACILITIES, EQUIPMENT, AND HUMAN RESOURCES**

### **Accomplishments**

Despite difficulties related to old buildings and infrastructure (e.g., the facility used to perform high-strain-rate testing, which had issues with a leaking roof), the staff has done an excellent job of maintaining equipment in working order. It has also improvised equipment for its specific needs. Some of the facility is rather old, but it is still functional. The facility also includes state-of-the-art electron microscopy. The Split Hopkinson Bar (for both tension and compression) is a state-of-the-art instrument, which also has fast recording capability (an infrared camera) for temperature measurements during rapid loading. Its Advanced Photon Source facility as well as its specialized mechanical testing of automotive parts is unique. This facility also has the ability to use X-ray beams directed at the center of a metal plate that is being deformed. This is particularly important to the automotive industry. Additionally, a liquid metal source X-ray instrument that uses liquid Ga-In alloy is among the key instrumentation within the MSED. There has also been great collaboration on X-ray synchrotron beam line use at different government facilities, primarily in the Department of Energy (DOE).

State-of-the-art instrumentation developments within the polymer-side of MSED include the resonant soft X-ray small angle scattering instrument; the modified MakerBot 3D printer; a novel three-in-one instrument that allows for correlations of polymer rheology with underlying microstructure and composition; an automated multifiber fragmentation machine; a microcapillary rheometer; and a layer-by-layer method for the highly controlled fabrication of model membranes for water purification.

In terms of human resources, the administrative support within the MSED consists of at least three highly experienced employees with 27 years of experience.

## Opportunities and Challenges

Aging structures and leaking roofs in some of the facilities is a major issue. Some strategic planning may be necessary to address these continuing issues. Building facilities need improvement in order to both improve safety and protect valuable equipment. Researchers have taken steps to do this by building metal shelters within rooms to protect equipment and experiments from rainwater damage and drastic humidity excursions during rain events. The issue of facility infrastructure is a challenging topic in buildings that are over 50 years old and during time periods of constrained budgets.

Additionally, the equipment for the empirical synthesis of materials is substantially less than best in the world. It would be advantageous to upgrade experimental (fabrication) capability and metallographic capability to match the MSED's computational and more advanced characterization capabilities. Last, the process of acquiring laboratory and computer equipment is still a challenge since the 2014 National Academies Assessment.

## DISSEMINATION OF OUTPUTS

### Accomplishments

The MSED staff members have been active in publishing in peer-reviewed high-impact journals. Based on the number of papers, and their publications in these journals, it is clear that the research work is being disseminated in an effective way. They are publishing in journals such as the *Journal of the American Chemical Society*, *Advanced Energy Materials*, *Nature-Scientific Reports*, *Advanced Materials*, *Physical Review Letters*, *ACS Nano*, and *Langmuir*. The Functional Nanostructured Materials Group has 81 reviewed research publications—which is an outstanding record of public dissemination of scientific results. In the polymers research focus, 27 permanent MSED staff produced approximately 240 publications in peer-reviewed journals and conducted 300 invited talks. This excellent productivity has been greatly enhanced by the presence of the National Research Council (NRC) postdoctoral fellows and research associates from all over the world. The Functional Polymers Group, the Polymers and Complex Fluids Group, and the Polymers Processing Group appear to be on the cutting edge in several technological areas and are best in the world in some. They have been able to maintain the excellent reputation of NIST in polymer science and engineering.

Other MSED dissemination activities include making and supplying standard materials, work delivered through Cooperative Research and Development Agreements (CRADAs), and achieving several external and internal recognitions. MSED leadership is very active in external organizations. Collaboration with the University of Chicago through CHiMaD seems to be going very well in several projects. There continues to be an excellent interaction of theory and modeling efforts with experiments. The MSED's contact and interaction with industrial and academic partners is also excellent. Active participation as leaders in standards organizations and specialized conferences has been especially notable and needs to be continued and encouraged.

There has also been substantial progress since the 2014 National Academies Assessment on improving external attendance at national and international conferences from both a financial and an administrative approval process perspective.

## Opportunities and Challenges

It would be useful to link with other electrochemical activities on other project teams. It would also be useful to utilize the postdoctoral network within NIST to identify linkages. There also appear to be opportunities to collaborate across many areas within the MSED, the MML, and other parts of NIST.

The quality of work within the MSED appears to be very good; however, during the review no information was given in some of the presentations and talks (e.g., the Thermodynamics and Kinetics Group's presentation) on how many papers were published, patents applied for, and presentations given at professional society meetings. A publications list was received upon request. Additionally, the presentations did not have citations to similar work (at other places). This makes it difficult to put the uniqueness of the MSED work in the correct context. It is important that citations to other work outside of NIST be included in the slides, as this omission was across the board.

Additionally, one of the main missions of NIST is to collaborate with outside researchers. The unique facilities and the expertise of NIST researchers are a clear draw and benefit for others. This leads to many collaborative papers. It is recommended that for the next National Academies Assessment, the published papers be listed in three categories: (1) papers solely authored by NIST researchers; (2) collaborative papers with outside researchers where the NIST researchers are major contributors; and (3) collaborative papers where NIST researchers have a supporting role. Such an approach will allow proper attribution representing the various roles that NIST plays in advancing the nation's science and technology.

## Office of Data and Informatics

### INTRODUCTION

The Material Measurement Laboratory (MML) established the Office of Data and Informatics (ODI) in 2014 right before the last National Academies Assessment in 2014. As a service-oriented organization, it focuses on creating a modern environment for data and informatics for the MML, as well as for its customers. The mission of the ODI is “to build the infrastructure for next-generation data science tools and the management of complex data sets needed to support scientific innovation and advance open data concepts.”<sup>1</sup> The ODI serves several functions which include the following: supporting national needs, such as the Materials Genome Initiative (MGI) and biological and chemical data integration, as well as the modernization of current NIST reference data services for use in state-of-the-art computer paradigms (i.e., virtual computing, parallel analysis, interoperability, semantic web, etc.) and the development of next-generation NIST reference data services. The ODI also facilitates MML’s adherence to the government’s open-data policy by providing guidance and assistance in the best practices for archiving and annotating research and data outputs. It also builds, concentrates, integrates, and coordinates capabilities needed to meet data challenges and leverage data-driven research opportunities (including Big Data and data.gov), particularly those that relate to the biological, chemical, and materials science communities within MML and, as the ODI grows, for all of NIST.<sup>2</sup> The 2014 National Academies Assessment recommended that the MML provide resources to the ODI as rapidly as possible. The MML management did an outstanding job adopting this recommendation and established data science and data management capabilities as one of the five goals for the MML. The ODI started with 5 dedicated staff members and limited dedicated funds. The ODI now has 22 staff members and a \$3 million budget. It is organized into two groups: the Data Services Group and the Data Sciences Group. The ODI is currently focused on four interrelated functional areas: modernization and curation of standard reference data (SRD); research data preservation and dissemination; in-house consultation services on informatics and analytics methods and tools; and open data/open science community engagement.

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<sup>1</sup> NIST Material Measurement Laboratory, “Material Measurement Laboratory Strategic Plan” <https://mmlstrategy.nist.gov>, accessed September 25, 2017.

<sup>2</sup> NIST Material Measurement Laboratory, “Office of Data Informatics,” <https://www.nist.gov/mml/odi>, accessed October 11, 2017.



## ASSESSMENT OF TECHNICAL PROGRAMS

### Accomplishments

The National Institute of Standards and Technology (NIST) SRD program has been a successful example of data generation, curation, and distribution in the chemical, biological, and materials sciences. The ODI has contributed to SRD delivery by modernizing the existing NIST reference data services, providing community consultation and support, and participating in the global open data science community. The ODI has provided guidance and assistance to the MML for archiving research data in order to meet government-mandated rules and regulations on open data. While some tools are MML-specific, others will be available to the broader scientific community. For example, it has already accomplished 10 percent of SRD modernization (and another 30 percent to come at the end of 2017) to improve user interfaces for web-based SRDs. Such improvements would make it possible for web-based SRDs to work on all computer platforms, would implement more consistent functionality, and would add application programming interfaces (APIs). It has also initiated internal reviews and solicited customer feedback on the entire SRD and special databases portfolio to set priorities for updating the remaining SRDs and eliminating obsolete products or products that can no longer be properly supported.

Additionally, it has engaged the Department of Commerce (DOC) Data Service Team for an SRD impact study, which is due in September 2018. It has also brought in *Socrata* to help build user interfaces and APIs, and it is making those available to research staff. This will enable the staff to make NIST reference data sets easier to search and download, both internally and externally, via the Internet. It has funded seven SRD enhancement projects for science groups with one-year seed money, with delivery expected in the summer of 2017.

The ODI developed a NIST-wide tool with the Office of Information Systems Management (OISM), called the Management of Institutional Data Assets (MIDAS), to simplify compliance. It captures key metadata and offers exports in standard formats, such as the Digital Object ID, uniform resource locator (URL), and enterprise data inventory record.

MIDAS supports automatic preservation to a NIST data repository that runs on NIST's Amazon cloud enclave. The ODI is also leading the effort in developing the NIST Data Science Portal for the dissemination of NIST's public data. Last, the ODI has been a representative for NIST in the International Chemical Identifier (InChI) Trust. The ODI established a consulting group for in-house consultation services on informatics and analytics methods and tools. In the areas of open data and open science community engagement, the ODI is an active contributor to many standards bodies and consortia and is starting to assume a leadership position in scientific data community.

### Opportunities and Challenges

Considering that the ODI was established only 3 years ago, it has made impressive progress. Since its conception, the ODI's technical activities have been largely focused more on data than on informatics. That is, their initial focus has been on implementing tools for producing curated, discoverable data sets, and ensuring their preservation. Now that they have succeeded in improving data access, it is time to work on tools that make the data more useful and easier to analyze. The MML needs to prepare a 3-year specific plan (roadmap) for the ODI to develop information and analytics tools. A roadmap will show management the importance of increasing their resources to enable informatics work and to solicit feedback from their customers on their plans, and a 3-year plan will enable the MML to show how the ODI will ramp up. In years 2 and 3, the ODI can obtain feedback from their customers that will enable them to do longer term planning.

More data sets and increasingly large ones are available in many science and engineering fields. Although data science has been around for quite some time, the tools and processes to learn from such scientific research data sets leave much to be desired. For example, there is a great need to enhance and

optimize the usability, discoverability, and interoperability of data. These needs create enormous opportunities for the ODI to establish NIST as a leader in data science and machine learning in biology, chemistry, and materials science. For example, one of the main projects in which the ODI is engaged is the Materials Genome Initiative (MGI) with the Materials Science and Engineering Division (MSED). Other projects and activities within the MML are also producing large amounts of data from which useful information could be extracted for learning. The ODI is in a great position to develop data informatics tools for manipulating complex data, as well as for mining that data to produce knowledge.

There is a lot of data and informatics activity in the majority of divisions within the MML (MSED, MMSD, CSD, BMD, and the ACMD). Right now, it appears that the MSED and MMSD have the most intimate engagement with the ODI through the MGI. It is a challenge to coordinate activities among different divisions within the MML to avoid duplicate efforts and different formats for the same information. On the other hand, coordinating and engaging with other data science efforts within the MML represents an opportunity for the ODI to learn the best practices and tools used by different divisions in handling data problems, and to share what they learn with all MML divisions.

The ODI is modernizing the delivery and e-commerce of SRD products to allow more automated access for customers. The experiences and knowledge learned through the modernization and curation of the SRD could be used to update other NIST products, such as the NIST Chemistry WebBook, which has been heavily utilized but still lacks an API that would make it easier to search and download, both programmatically and via a web browser.

In response to the federal policy mandate on open data, the ODI is helping to develop data management plans (DMPs) for the MML and building an infrastructure for data preservation and curation. The ODI could become directly involved in other major NIST programs, such as the Manufacturing Extension Partnership (MEP), to engage the internal and external customers for data challenges, including data plans, data preservation, and curation.

The ODI has made important progress in the modernization of SRDs for easy access and delivery. As soon as SRD projects are under control, the ODI could start developing a repertoire of analytics tools.

## **PORTFOLIO OF SCIENTIFIC EXPERTISE**

### **Accomplishments**

The ODI has assembled a strong team with complementary expertise in scientific data management, materials science, informatics, and analytics. In particular, the director of the ODI is a recognized authority in scientific data management for astronomy, which is a poster child for state-of-the-art scientific data management. He brought two members of his team from the Virtual Observatory at Johns Hopkins.

### **Opportunities and Challenges**

The ODI currently has only two people available to develop and support the data informatics effort, while there are extensive needs for such efforts in the MML. The completion of SRD modernization will free up some staff for this activity. However, even more staff members will be needed to devote their efforts to informatics.

While the data infrastructure is being built, the logical next step is to fully utilize the infrastructure for data-driven science. Therefore, the ODI needs to ramp up its effort to build the data informatics and analytics capabilities to handle increasingly complex and data-driven research challenges. There are many data and informatics activities among the different divisions. Therefore, to address these research challenges, the ODI needs to take advantage of informatics, analytics, and statistics expertise in these other groups at NIST.

## **ADEQUACY OF FACILITIES, EQUIPMENT, AND HUMAN RESOURCES**

### **Opportunities and Challenges**

Data preservation is useless unless there is enough associated metadata to enable interpretation of the data years later. The same issue applies to publishing data to satisfy the open data mandate. However, it is tedious to capture and record that metadata manually. To avoid that manual effort and to free up scientists to do science, it would be beneficial if there were an automated system that captures the metadata from instruments and associates it with the data. Therefore to facilitate the data preservation and meet the open data mandate required for government agencies, the ODI needs to acquire or develop a Laboratory Information Management System (LIMS). Such a system could pull metadata with data from instruments, which would make such data easy to transform into publishable data.

The ODI also needs to be provided with sufficient office space for staff, and with the support necessary to modernize its computing facility.

## **DISSEMINATION OF OUTPUTS**

### **Accomplishments**

The ODI is on the verge of delivering some of its first major products. For example, it has developed initial capabilities for data preservation and dissemination in the Open Access to Research (OAR) project. As part of the NIST MGI effort, it is operating the Material Measurement Laboratory Repository Server,<sup>3</sup> which is a data repository for data sharing. It is also developing the NIST Materials Resource Registry, a federated network of catalogs containing information about materials science resources that will be delivered in the summer of 2017. Furthermore, in collaboration with the Information Technology Laboratory (ITL), it has deployed and released several versions of the Materials Data Curation System (MDCS) for capturing, sharing, and structuring the materials data.

### **Opportunities and Challenges**

The ODI needs to invest time in standards activities and consortia to establish NIST as a leader in scientific data management.

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<sup>3</sup> For the repository, go to “Material Measurement Laboratory Repository Server,” updated October 29, 2013, at <http://materialsdata.nist.gov/>.

## Office of Reference Materials

### INTRODUCTION

The Office of Reference Materials (ORM) is the unit within the Material Measurement Laboratory (MML) that provides the marketing, sales, and distribution of all the National Institute of Standards and Technology (NIST) standard reference materials (SRMs) and standard reference instruments (SRIs). The office conducts all business-related functions to support this mission for NIST. These include the administration, product packaging, customer and technical support, quality control and assurance, management of e-commerce infrastructure, and all related documentation associated with SRMs and SRIs. Customers use NIST SRMs to support measurements in industrial manufacturing processes, clinical genomics, environmental analysis, health measurements, and basic measurements in science and metrology. Industry adoption and reference to NIST SRMs is a vitally important mechanism for supporting measurement traceability in the United States. The ORM currently offers a catalog of approximately 1,200 SRMs that possess well-characterized and well-documented composition and properties. ORM customers purchase these products to perform instrument calibrations, verify the accuracy of specific measurements, and support the development of new measurement methods as part of their overall quality assurance programs. The ORM client base includes industry, academia, and government. The ORM bins their SRMs into 31 separate categories including environmental, metals, high-purity materials, fuels, forensics, health and clinical, and industrial hygiene. The ORM has a very important and public-facing role for NIST that enables the organization to fulfill its measurements and standards mission.

The organization of the ORM resembles a structure similar to an e-commerce organization. The office director and staff provide oversight of all ORM operations and group activities and serve as the primary interface with the MML division chiefs to construct and execute the SRM development strategy. The division director also administers the service development (SD) and working capital funds (WCFs) that support the creation and production of new SRM product offerings. Several groups in the ORM report to the office director, including the Business Application Development, Support, and Security Group (BADSS), which oversees sales, cataloging, and inventory systems and is responsible for cybersecurity and compliance with all applicable Department of Commerce (DOC) and federal government regulations regarding the use of information technology (IT) for sales and support of the SRM program; the Materials and Physical Services Group, which is responsible for sample and product preparation, homogenization, packaging, order support, and shipping of all SRM products; the Sales and Customer Services Group, which manages customer orders received by phone, e-mail, Internet, and fax, and is also assigned matters and country-specific requirements pertaining to export requirements associated with international sales; the Publication and Web Services Group, which has the responsibility for all documentation of products, including SRM certificates contained on the NIST SRM website, and also for maintaining expertise in the accurate labeling of ORM products and conformity to the Globally Harmonized System (GHS) rules for labeling hazardous materials; and the Business and Quality Management Group, which oversees and implements quality processes that document the quality system, produces quality reports (quarterly) to the NIST quality manager, and maintains ORM adherence to ISO 9001.

## ASSESSMENT OF TECHNICAL PROGRAMS

### Accomplishments

Due to the nature and mission of the ORM, the assessment of its technical programs needs to adopt a different lens from those used to examine the MML research divisions. The office largely functions as a self-supporting e-commerce activity housed within a research organization. The organization of the ORM, its staff, and its facilities are structured to efficiently and effectively produce, maintain, sell, and ship SRMs and SRIs. Its scientific and technical programs associated with the development of new SRMs and production of existing SRMs are performed in partnership with NIST research entities in the MML. The metrics used for assessing its activities necessarily need to be different from those used to assess the research divisions.

Using these measures, the ORM can list a number of accomplishments that are aligned with its mission and programmatic goals. The number of sales of SRM products totals approximately 32,000 units per year, resulting in roughly \$19.5 million in income. The sales group of six people and one group leader fields more than 50,000 customer inquiries per year, including requests for quotes and technical information. The top five sales products include the following: 2092 Low-Energy Charpy V-Notch, 2096 High-Energy Charpy V-Notch, 1196 Standard Cigarette for Ignition Resistance, 84L Potassium Hydrogen Phthalate, and 1849A Infant/Adult Nutritional Formula. The customer base for ORM products consists of 50.1 percent U.S. industry; 43.5 percent international industry; 2.3 percent U.S. federal government; and 2.7 percent state and local governments across all major industrial sectors. International sales have been increasing steadily and now account for nearly half of all sales. The customer satisfaction appears high, as exemplified by the fact that less than 0.5 percent of items sold are returned for any reason.

Proper labeling and hazard assessment for ORM products is a significant and important technical responsibility of the office. The shipped products need to comply with the GHS for labeling materials. Further, this new regulation requires that the staff of the ORM publications and Internet services also maintains expertise in these labeling requirements. The ORM deployed two of its Ph.D. inorganic chemists and an expert in Department of Transportation (DOT) regulations to produce new GHS-compliant labels for over 800 products.

The ORM conducts an extensive quality assurance program to support its operations. It has appropriately deployed the necessary staff and processes in their organization to make its quality assurance programs successful. The quality assurance program is extensive and extends to every facet of the operations. The group is ISO 9001 certified and well connected to the NIST-wide Quality Manager.

### Opportunities and Challenges

The group is highly focused, customer-centric, and very aligned with NIST's fundamental mission. Its SRM products are valued by industry customers and directly contribute to U.S. commerce. The *truth in a bottle* that is produced by the ORM through its SRM portfolio provides the necessary market confidence in the production and sale of products across nearly every sector of the economy and has worldwide impact. The interfaces to NIST research divisions provide access to measurement science capabilities that are among the best in the world, as well as the ability to create new reference methods (RMs) as they are needed by industry. Further, the team recognizes the ORM's growth in international sales and has identified opportunities to partner with licensed distributors to better serve these customers in more effective and efficient ways. The office also uses its ability as a convener to bring industry interests together to solve common issues facing a specific product type or measurement need, as exemplified by the work performed on infant nutritional formula SRMs.

At the same time, the ORM faces several challenges and possible risks. For example, the office receives the vast majority of its sales from a very small number of products (Charpy Bars, Standard Cigarettes, Potassium Hydrogen Phthalate, etc.). Any significant disruption in demand for these popular

products will have an adverse effect on the operations of the ORM, and more importantly, on the ability to develop new SRMs for emerging industries and applications. This risk is accompanied by the fact that the current allocation of WCFs and service development (SD) funding given to the research divisions is already limited and increasingly used to support recertification of existing products versus developing new SRMs.

The ORM appears to be a highly successful operation that directly supports the mission of NIST and U.S. commerce overall. Yet, the ORM operates much differently from the other units within MML and NIST overall. It does not conduct the type of research performed by MML divisions, and the majority of ORM work involves managing and maintaining the SRM sales business that includes marketing, production, sales, quality control, e-commerce, packaging, and distributions. The emerging partnership with the University of Maryland (UMD) and similar efforts with other external institutions to examine marketing and customer engagement strategies is laudable. At the same time, the ORM needs to consider an external examination of its overall business practices, the adequacy of its e-commerce tools, the effectiveness of its marketing and sales operations, and other pertinent areas related to its operations.

The current allocation of WCFs and service development funds is increasingly assigned to support recertification and production of existing product lines. This situation may present a risk to ORM and its ability to produce new materials needed by emerging applications and industrial sectors. The MML needs to develop a strategy to optimize and prioritize the balance between existing product support and the research, production, and certification of new SRMs within the ORM.

Packaging and distribution is a significant portion of ORM operations. Appropriate packaging, handling, and long-term storage of SRM materials are critical to the ORM mission. Existing capabilities are being stretched to their limit, and in some cases may not be adequate for anticipated product offerings. In particular, biomaterial SRMs will have unique and important shelf-life considerations that need to be examined for these products. The MML needs to undertake an effort to benchmark the state of the art in industrial packaging and storage methods and develop a packaging modernization plan to support the ORM catalog of materials.

## **PORTFOLIO OF SCIENTIFIC EXPERTISE**

### **Accomplishments**

The portfolio of expertise of the ORM is aligned with its mission as a stand-alone business unit and is not easily compared to other MML divisions. Of the 38 staff members in the ORM, 34 percent are scientists, 24 percent are technicians, and 34 percent provide administrative or other program support. And so, the majority of ORM staff cannot be measured using similar metrics or measures. At the same time, the scientific and technical staff housed in the ORM work closely with peers in research divisions to produce and document existing SRMs and perform the necessary research and measurements to create new SRM products as they are needed by industrial customers. By all indications, the ORM technical staff is highly qualified, enthusiastic, and able to perform its jobs very well. This interface is important and provides a significant link between the research divisions. It also provides an important mechanism for NIST to have a positive impact on industrial commerce through measurement science and standards.

### **Opportunities and Challenges**

Business-to-business commerce is rapidly evolving across the economy as advances in technology affect business practices ranging from marketing, to online sales, to distribution. The ORM is not immune to these macro-level effects that may alter the expectations of its customer base. At the same time, the increased level of international sales places new and unique challenges on the ORM staff, who navigate a variety of issues associated with exporting ORM products all over the world. The use of overseas licensed

vendors to market and distribute ORM SRM products is commendable and presents a real opportunity to expand its international sales. Further, these macro-level operations may motivate an examination of current staffing strategies; emerging demand for new knowledge, skills, and abilities aligned to modern e-commerce operations; and possible opportunities for reengineering positions when positions become vacant.

The development of new SRMs is a lengthy and arduous process that requires great effort over several years. The ORM develops new SRM products with very limited resources in partnership with the research divisions. Effective and efficient use of ORM researchers and research staff from the research divisions are essential to the process. These partnerships have been, and continue to be, largely effective, as evidenced by the adoption of new SRMs on a frequent basis. Yet, the research performed to create these new products rarely results in highly cited publications in archival journals. And so, researchers may view SRM work as misaligned with their performance incentives within the divisions. Further, it appears that highly qualified research scientists may often perform much of the necessary yet labor-intensive and lower-level laboratory work associated with these efforts that may be better performed by laboratory technicians. These issues may discourage outstanding research staff to work on the development of SRMs and hinder the ORM's ability to provide new products as demand emerges from industry.

As part of a business operations review, the MML needs to examine current staffing and benchmark it against comparable e-commerce operations to create a strategic workforce development and staffing plan.

The MML also needs to examine current staffing structures associated with recertification of existing products and the development of new SRMs to more appropriately assign tasks to research and technician staff, and to encourage SRM-related work as part of the overall measurement science mission of the organization.

## **ADEQUACY OF FACILITIES, EQUIPMENT, AND HUMAN RESOURCES**

### **Accomplishments**

The ORM relies on the analytical and research facilities in the research divisions to make appropriate measurements in support of the production and sale of SRMs. This includes a variety of analytical instrumentation needed to quantitatively measure the properties of SRMs and the associated uncertainties in those measurements. Further, the ORM operates a very large warehouse and distribution operation that entails storage, packaging and labeling, and shipping of SRMs to customers located around the globe. The variety of packaging and storage facilities varies greatly to match the breadth of products in the ORM catalog. These include warehouses for bulk chemical and metal storage as well as environmentally controlled containers to store perishable biological materials safely.

### **Opportunities and Challenges**

Many of the analytical instruments that are critical to the certification of SRMs are dated and do not represent the state of the art. While these instruments are still able to perform their functions, there are commercially available upgrades that may increase the efficiency and effectiveness of the analysis and characterization of SRMs. Additionally, many of these measurements and instruments lend themselves to automation, which may reduce the burden on research staff to perform routine labor-intensive tasks.

The MML needs to conceive and implement a plan for replacing, refurbishing, and maintaining analytical laboratory instrumentation housed within the research divisions that support the certification of SRM materials.

Further, the space and facilities needed to store biological materials appears to be reaching a limit in the current warehouse. As the breadth and number of perishable biological items increases, finding

appropriate storage facilities and containers may become a significant challenge. The MML needs to develop and implement a plan to accommodate growth in storage needs associated with perishable biological materials.



## Conclusions and Recommendations

### GENERAL CONCLUSIONS AND RECOMMENDATIONS

Across the MML divisions, many salient themes were identified regarding the high technical quality of the research, excellence of the scientific staff, strong customer outreach and scientific collaboration, and strong publication and dissemination activities.

While the recommendations below are grouped by divisions to provide actionable suggestions that address each division's unique needs (a focal point of this review), several crosscutting themes, as well as suggestions and recommendations that are thematically similar, were also identified that pointed to opportunities across, or within, the divisions. Specifically, in some of the divisions, such as the ACMD, BMD, and the MMSD, there is an opportunity to take a closer look at balance between long-term goals/research and short-term projects. Such an analysis could help to establish a balanced portfolio of research, as well as maximize the division's manpower and resources. In the case of the inclusion of long-term or high-impact research, it could also help to enable the next generation of measurement tools.

Additionally, some of the NIST staff noted that there was a lack of sufficient technical staff within some of the divisions. This lack of technical support has caused some Ph.D. scientists to do routine tasks like equipment maintenance, which is a poor use of their skills and limits productivity. There was also a concern that postdoctoral fellows have to spend a lot of time learning equipment maintenance and troubleshooting. This can potentially lead to an inefficient use of the postdoctoral fellows, and may also impede their progress toward career goals in research. Also, administrative staff is limited in some areas, and this is causing Ph.D. scientists to do administrative tasks required for their research and development (R&D) work.

It was also noted that the facilities in several divisions, such as the BBD, BMD, CSD, and MSED, are aging and outdated. Some of these facilities have leaking roofs and poor ventilation systems, which makes them inadequate for conducting particular experiments, and limits the range of research that can be performed in those laboratories. Routine requests for maintenance can, in some cases, also take a long time to be addressed.

It was also identified that some divisions, such as the BBD, BMD, and MMSD, could benefit from expanding their working relationships with the Office of Data and Informatics (ODI). Substantial benefits related to data management, leveraging developments made by the divisions, and the establishment of best practices may be realized by pursuing efforts such as these that cross division boundaries.

The review also identified opportunities to better utilize the postdoctoral fellows as well as their network. For example, it was identified that CSD has the opportunity to increase the number and quality of National Institute of Standards and Technology and National Research Council (NRC) postdoctoral fellows within their division. Another opportunity that was identified was through leveraging the postdoctoral fellows' network to improve connectivity across NIST.

Along with suggestions throughout the report, several of the divisional recommendations below reflect these crosscutting or thematically similar topics. Recommendations 1 and 3 both address the theme of finding a balance between long-term goals and research and short-term projects within the ACMD and the BMD—a challenge that was also pointed out in the MMSD chapter. Recommendation 12 focuses on increasing technical and administrative staff in the CSD, which reflects a similar suggestion in body of

the report that MMSD also increase technician support. Recommendations 7 and 10 both address facility maintenance in the BMD and the BBD, a topic that was highlighted in the CSD and MSED chapters. Recommendation 6 (which focuses on the BMD) and Recommendation 20 look at expanding the role of the ODI within divisions that have significant data science efforts, a suggestion that is also echoed in the BBD and MMSD chapters. Recommendations 13 and 15 both focus on improving the use of postdoctoral fellows in the CSD and the MMSD. Given that many of these recommendations and suggestions are thematically similar or crosscutting, it may be helpful for MML leadership (divisional leaders, etc.) to meet together to review these suggestions as a whole and to determine where solutions in other divisions may have already been rendered.

### **Applied Chemicals and Materials**

The programs in the ACMD are well thought out and are starting to fit together as the division refines its focus. Some opportunities within the division, such as those in the Fatigue Fracture Group, are associated with finding research efforts that fit with the mature efforts in the group to allow a full spectrum of projects—from mature to high-risk. Further efforts to have a broader range of projects across the high-risk to mature continuum would better position the division to have the available resources and pathways to address critical problems.

**RECOMMENDATION 1: The Material Measurement Laboratory should consider expanding its efforts in such a way that the Applied Chemicals and Materials Division’s projects will span the range of development—from high-risk research to mature support programs.**

While the ACMD is doing an excellent job with their dissemination efforts, one way they could facilitate more dissemination is through an exchange program between ACMD personnel and other organizations in industry, universities, and national laboratories. These exchanges could be both to and from the ACMD, with the ultimate goal of expanding dissemination and enhancing the staff.

**RECOMMENDATION 2: The Material Measurement Laboratory should consider an exchange program between the Applied Chemicals and Materials Division personnel and other organizations in industry, universities, and national laboratories.**

### **Biomolecular Measurement**

The BMD excels at addressing the critical measurement needs of the United States in key areas involving biomolecular technologies, including mass spectroscopy, DNA forensics, and biopharmaceuticals. This impact is derived from close interaction with industry and federal agencies. It is important for the division to balance this immediate focus against the upsides of long-term and high-impact research aimed at enabling the next generation of measurement tools, which could lead to potentially revolutionary advances in future measurement. It was evident that some groups within the BMD were pursuing this type of long-range research (e.g., efforts aimed at the development of methods for single-molecule protein sequencing), and these efforts could be expanded across all groups in the BMD.

**RECOMMENDATION 3: The Material Measurement Laboratory should consider promoting a balanced portfolio of short-term and long-term activities in all groups across the Biomolecular Measurement Division.**

The BMD has identified the compelling need for new measurement standards and methods in the area of precision medicine. It is important to develop a clear set of goals concerning this research in precision medicine and a roadmap for achieving these goals. This roadmap would include the prioritization of target selection for relevancy (e.g., protein biomarkers) and maximizing opportunities for collaboration across NIST (e.g., with the BBD).

**RECOMMENDATION 4: The Material Measurement Laboratory should consider developing a roadmap to realize a program in precision medicine that addresses short-term and long-term needs and maximizes opportunities for collaboration across the National Institute of Standards and Technology.**

The interactions of the BMD with the University of Maryland (UMD) through the Institute for Bioscience and Biotechnology Research (IBBR) have led to synergies between the UMD and NIST. A roadmap is needed to ensure that this productive interaction continues into the future in a manner aligned with the goals of the BMD. This roadmap needs to include the commitment of the UMD to place faculty with aligned research interests in the IBBR. It also needs to describe the role of the IBBR in the context of the strategic goals of the BMD in order to establish new capabilities and expertise to enable protein production, to contribute to the National Institute for Innovation in Manufacturing Biopharmaceuticals (NIIMBL), and to broadly impact biopharmaceutical manufacturing initiatives through improved measurement.

**RECOMMENDATION 5: The Material Measurement Laboratory and the Institute for Bioscience and Biotechnology Research (IBBR) should consider establishing a roadmap that describes the role of the IBBR in the context of the strategic goals of the Biomolecular Measurement Division.**

The multiple divisions of the MML have shared goals (e.g., precision medicine for the BMD and the BBD) and shared capabilities (e.g., genomics in the BMD and the BBD). Groups within the divisions have complementary expertise to address challenges related to data analysis and management. There are, however, relatively few examples of crosscutting interactions that realize these potential synergies between divisions and between the groups of the divisions. The BMD needs to consider creating incentives and mechanisms to stimulate cross-group and cross-division interactions that could create new and existing programmatic synergies between the informatics efforts of the BMD and the ODI, and between the genomic and precision medicine efforts of the BMD and the BBD.

**RECOMMENDATION 6: The Material Measurement Laboratory should consider creating incentives and mechanisms to stimulate cross-group and cross-division interactions between the Biomolecular Measurement Division and the Office of Data and Informatics, and between the genomic and precision medicine efforts of the Biomolecular Measurement Division and the Biosystems and Biomaterials Division.**

The laboratories in which the BMD is located on the main NIST campus are old, and there is a constant need for renovation and maintenance (e.g., to address leaking ceilings). Routine requests for maintenance take a very long time, in some cases months, to be addressed. NIST needs to further improve internal processes for approval and execution of requested maintenance needs in order to protect investments in complex and sensitive instrumentation within the BMD.

**RECOMMENDATION 7: The Material Measurement Laboratory should consult with management of the National Institute of Standards and Technology to consider improving internal processes for approval and execution of requested maintenance needs within the Biomolecular Measurement Division.**

The BMD's website for SRMs is not currently organized around the needs of industry users. It could be reorganized to present SRMs grouped according to industries served by the SRMs (clinical diagnostics, biopharmaceutical, etc.). This has the potential to increase the use of SRMs, increase cost recovery for preparation of SRMs, and communicate to stakeholders the important role that NIST plays in enabling the competitiveness of U.S. industry and commerce. In addition, it will facilitate the adoption of SRMs that are new and not widely known to potential users.

**RECOMMENDATION 8: The Material Measurement Laboratory should consider evaluating the benefits of an improved Biomolecular Measurement Division website that markets standard reference materials for specific industries and federal agencies.**

### **Biosystems and Biomaterials**

The BBD has many ongoing projects and achievements, conducted within and outside of NIST. The BBD staff works closely with other MML divisions. Overall, the division possesses a high level of technical skills and works on cutting-edge science that requires both RMs and standards. The 101 staff members perform work in many areas. The division overall is lean in technical staff but has a superb group of Ph.D. scientists at all levels, from junior to very senior fellows. BBD scientists are conducting outstanding science. Key technical expertise in specialized instrumentation, however, has been lost and not replaced.

**RECOMMENDATION 9: The Material Measurement Laboratory should make a concerted effort to maintain continuity in the staffing of critical positions within the Biosystems and Biomaterials Division.**

Some of NIST's laboratory infrastructure is not adequate for conducting particular experiments crucial to the BBD mission, such as a cell culture up to Biosafety Level 2 (BSL-2) standards. This is owed to dust in older ducts and excess storage in laboratory space.

**RECOMMENDATION 10: The Material Measurement Laboratory should consider engaging with NIST's central operations to find ways to improve the Biosystems and Biomaterials Division's building infrastructure.**

Equipment has an institutional overhead cost of 50 percent to pay for human resources and safety. BBD staff indicated that equipment taxes significantly reduce the amount of equipment they can purchase.

**RECOMMENDATION 11: The Material Measurement Laboratory should consider engaging with NIST's central operations to find ways to minimize the Biosystems and Biomaterials Division's overhead burden.**

### **Chemical Sciences**

In total, 115 scientific staff members and approximately 50 associates in the CSD are supported by only 4 technicians and 8 support staff. As a result, Ph.D. scientists are doing most of the laboratory work that could be done by technicians. They are also executing most of the administrative tasks required for their R&D work. To increase the productivity and satisfaction level of its scientific staff, the CSD could provide administrative support for nonscientific tasks and technician support for laboratory work and data analyses that do not require Ph.D. training.

**RECOMMENDATION 12: The Material Measurement Laboratory should consider increasing the Chemical Sciences Division’s support staff both for administrative tasks and for technician support.**

The CSD could maximize the number and quality of NIST and NRC postdoctoral fellows arriving in the division. There are currently no NIST fellows in the CSD and only three of the CSD’s eight groups have an NRC postdoctoral fellow—three in one group, and one in each of the other two groups. The uneven distribution of these fellows among CSD groups and among MML divisions suggests that only a few people are utilizing the best methods for attracting excellent postdoctoral researchers.

**RECOMMENDATION 13: The Material Measurement Laboratory should consider maximizing the number and quality of National Institute of Standards and Technology and National Research Council postdoctoral fellows within the Chemical Sciences Division.**

### **Materials Measurement Science**

The MMSD’s competency database is a good idea; however, the division needs to leverage other databases, such as publications and presentations, from which keywords could be extracted.

**RECOMMENDATION 14: The Material Measurement Laboratory should consider leveraging other databases outside of the Materials Measurement Science Division’s competency database.**

Within the MMSD there needs to be transparency of how to succeed, especially for early career staff. One way to do so is to leverage NIST’s postdoctoral network with a professional development program. Such a program could help to improve connectivity across NIST.

**RECOMMENDATION 15: The Material Measurement Laboratory should consider leveraging the National Institute of Standards and Technology’s postdoctoral network with a professional development program in order to improve connectivity across NIST.**

The MMSD largely excels in the rigor of the data it collects, through applying statistical analysis to optimize the quality of its data and conclusions. One challenge is in the consistency of applying experimental design and statistical analysis across all groups. Uniform application of experimental design (when the project is conducive to it) and statistical analysis is needed. Particularly for exploratory work, the design of experiments would improve efficiency in determining salient variables to explore.

**RECOMMENDATION 16: The Material Measurement Laboratory should consider making the application of the Materials Measurement Science Division’s experimental design and statistical analysis more uniform in order to improve the efficiency in determining salient variables to explore.**

### **Materials Science and Engineering**

The MSED is among the best in the world in terms of computational techniques and researchers. Although the staff is highly knowledgeable, laboratory equipment for making, processing, and to a lesser extent, preparing metallic alloys for testing are basic (with the exception of a new melt spinner for high solidification rate processing of metals). Numerous other facilities worldwide have better metallic processing laboratory equipment.

**RECOMMENDATION 17: The Material Measurement Laboratory should consider updating the Materials Science and Engineering Division’s laboratory equipment used for making, processing, and preparing metallic alloys for testing.**

#### **Office of Data and Informatics**

Since its conception, the ODI’s technical activities have been largely focused more on data than on informatics. Now that they have succeeded in improving data access, it is time to work on tools that make the data more useful and easier to analyze. A roadmap is now needed to show management the importance of increasing their resources to enable informatics work and to solicit feedback from their customers on their plans. The MML needs to prepare a 3-year roadmap for the ODI to develop information and analytics tools. A 3-year plan will enable the MML to show how the ODI will ramp up. In years 2 and 3, the ODI can obtain feedback from their customers that will enable it to do longer term planning.

**RECOMMENDATION 18: The Material Measurement Laboratory should prepare a 3-year roadmap for the Office of Data and Informatics to develop information and analytics tools.**

Data preservation is useless unless there is enough associated metadata to enable interpretation of the data years later. The same issue applies to publishing data to satisfy the open data mandate. However, it is tedious to capture and record that metadata manually. To avoid that manual effort and to free up scientists to do science, it would be beneficial if there were an automated system that captures the metadata from instruments and associates it with the data. Therefore, to facilitate data preservation and meet the open data mandate required for government agencies, the ODI needs to acquire or develop a Laboratory Information Management System (LIMS) in order to pull metadata with data from instruments. This would make such data easy to transform into publishable data.

**RECOMMENDATION 19: The Material Measurement Laboratory should consider acquiring or developing a Laboratory Information Management System (LIMS) for the Office of Data and Informatics.**

There has been strong engagement between the ODI, the MSED, and the MMSD through the Materials Genome Initiative (MGI) program. However, there are many other significant data science efforts in divisions within the MML that could be engaged by the ODI. The ODI needs to coordinate and engage with other data science efforts within the MML to learn their best practices in data preservation, curation, and informatics, and to share that learning with all of the MML.

**RECOMMENDATION 20: The Office of Data and Informatics should engage divisions within the Material Measurement Laboratory that have significant data science efforts in order to learn their best practices in data preservation, curation, and informatics, and to share that information with the rest of the Material Measurement Laboratory.**

#### **Office of Reference Materials**

The ORM appears to be a highly successful operation that directly supports the mission of NIST and U.S. commerce overall. The ORM operates much differently from the other units within the MML and NIST. It does not conduct the type of research performed by MML divisions, and the majority of the ORM work involves managing and maintaining the SRM sales business that includes marketing,

production, sales, quality control, e-commerce, packaging, and distributions. The emerging partnership with the UMD to examine marketing and customer engagement strategies, and similar efforts with other external institutions, is commendable. At the same time, the ORM needs to consider an external examination of its overall business practices, the adequacy of its e-commerce tools, the effectiveness of its marketing and sales operations, as well as other pertinent areas related to its operations.

**RECOMMENDATION 21: The Material Measurement Laboratory should consider an external examination of the Office of Reference Materials' overall business practices, the adequacy of its e-commerce tools, the effectiveness of its marketing and sales operations, and other pertinent areas related to its operations.**

The current allocation of working capital funds (WCFs) and service development funds is increasingly assigned to support recertification and production of existing product lines. This situation may present a risk to the ORM and its ability to produce new materials needed by emerging applications and industrial sectors. The MML needs to develop a strategy to optimize and prioritize the balance between existing product support and the research, production, and certification of new SRMs.

**RECOMMENDATION 22: The Material Measurement Laboratory should develop a strategy for the Office of Reference Materials to optimize and prioritize the balance between existing product support and the research, production, and certification of new SRMs.**

Packaging and distribution is a significant portion of the ORM operations. Appropriate packaging, handling, and long-term storage of SRMs are critical to the ORM mission. Existing capabilities are being stretched to their limit, and in some cases, may not be adequate for anticipated product offerings. NIST needs to undertake an effort to benchmark the state-of-the-art in industrial packaging and storage methods and develop a packaging modernization plan to support the ORM catalog of materials.

**RECOMMENDATION 23: The Material Measurement Laboratory should consider undertaking an effort to benchmark the state of the art in industrial packaging and storage methods and develop a packaging modernization plan to support the Office of Reference Materials catalog of materials.**

As part of a business operations review, the MML needs to examine current staffing and benchmark it against comparable e-commerce operations. Such an analysis would be performed in order to craft a strategic workforce development and staffing plan.

**RECOMMENDATION 24: The Material Measurement Laboratory should examine current staffing in the Office of Reference Materials and benchmark it against comparable e-commerce operations to create a strategic workforce development and staffing plan.**

The MML needs to examine current staffing structures in the ORM that are associated with the recertification of existing products and the development of new SRMs in order to more appropriately assign tasks to research and technician staff, and to encourage SRM-related work as part of the overall measurement science mission of the organization.

**RECOMMENDATION 25: The Material Measurement Laboratory should examine current staffing structures in the Office of Reference Materials that are associated with recertification of existing products and the development of new standard reference materials to more appropriately assign tasks.**

Many of the analytical instruments that are critical to the certification of SRMs within the ORM are

dated and do not represent the state of the art. There are commercially available upgrades that may increase the efficiency and effectiveness of the analysis and characterization of SRMs. Many of these measurements and instruments lend themselves to automation, which may reduce the burden on the research staff to perform routine labor-intensive tasks.

**RECOMMENDATION 26: The Material Measurement Laboratory should conceive and implement a plan for replacing, refurbishing, and maintaining analytical laboratory instrumentation housed within the Office of Reference Materials that supports the certification of standard reference materials.**

The space and facilities in the ORM that are needed to store biological materials appears to be reaching a limit in the current warehouse. As the breadth and number of perishable biological items increases, finding appropriate storage facilities and containers may become a significant challenge.

**RECOMMENDATION 27: The Material Measurement Laboratory should develop and implement a plan to accommodate growth in the Office of Reference Materials' storage needs that are associated with perishable biological materials.**





## **Appendixes**



**A**

**Material Measurement Laboratory Staffing in Fiscal Year 2017**

TABLE A.1 Material Measurement Laboratory (MML) Staffing in Fiscal Year 2017

<b>Division/Laboratory</b>	<b>Staff type</b>	<b>Number During FY2017</b>
<b>OVERALL STAFFING IN THE MML</b>		
	Scientist	507
	Technician	36
	Admin	27
	Support	45
	Fellows	9
	Associates	295
	Total	919
<b>APPLIED CHEMICALS AND MATERIALS DIVISION</b>		
	Scientist	51
	Technician	4
	Admin	0
	Support	4
	Fellows	1
	Associates	16
	Total	76
<b>BIOSYSTEMS AND BIOMATERIALS DIVISION</b>		
	Scientist	48
	Technician	3
	Admin	0
	Support	4
	Fellows	0
	Associates	46
	Total	101
<b>BIOMOLECULAR MEASUREMENT DIVISION</b>		
	Scientist	67
	Technician	6
	Admin	0
	Support	5
	Fellows	2
	Associates	30
	Total	110
<b>CHEMICAL SCIENCES DIVISION</b>		
	Scientist	115
	Technician	4
	Admin	0
	Support	8

	Fellows	0
	Associates	45
	Total	173
<b>MATERIALS MEASUREMENT SCIENCE DIVISION</b>		
	Scientist	96
	Technician	5
	Admin	0
	Support	7
	Fellows	3
	Associates	65
	Total	176
<b>MATERIALS SCIENCE AND ENGINEERING DIVISION</b>		
	Scientist	82
	Technician	2
	Admin	2
	Support	6
	Fellows	2
	Associates	80
	Total	194
<b>OFFICE OF DATA AND INFORMATICS</b>		
	Scientist	13
	Technician	0
	Admin	4
	Support	2
	Fellows	0
	Associates	3
	Total	22
<b>OFFICE OF REFERENCE MATERIALS</b>		
	Scientist	13
	Technician	9
	Admin	10
	Support	3
	Fellows	0
	Associates	3
	Total	38

SOURCE: NIST Material Measurement Laboratory, "Made to Measure: Building the Foundation for Tomorrow's Innovation in the Biological, Chemical and Material Sciences," read-ahead to the panel, May 9, 2011, pp. 14, 38, 47, 58, 77, 97, 114, 135, and 157.

## B

### Acronyms

AAFS	American Academy of Forensic Sciences
ACMD	Applied Chemicals and Materials Division
ACS	American Chemical Society
AFM	atomic force microscopy
AM Bench	Additive Manufacturing Benchmark Test Series
AMAP	Arctic Monitoring and Assessment Programme
API	application programming interface
APS	American Physical Society
ARMI	Advanced Regenerative Manufacturing Institute
ARPA-E	Advanced Research Projects Agency-Energy
ASM	American Society of Materials
ASTM	American Society for Testing and Materials
ASTMi	American Society for Testing Materials International
ATB-MII	Advanced Tissue Biofabrication Manufacturing Innovation Institute
ATCC	American Type Culture Collection
BADSS	Business Application Development, Support, and Security Group
BBD	Biosystems and Biomaterials Division
BCARS	broadband coherent anti-Stokes Raman scattering
BMD	Biomolecular Measurement Division
BSL-2	Biosafety Level 2
CALPHAD	Computer Coupling of Phase Diagrams and Thermochemistry
CDC	Centers for Disease Control
cGMP	current Good Manufacturing Practices
CHiMaD	Center for Hierarchical Materials Design
CLL	chronic lymphocytic leukemia
CNST	Center for Nanoscale Science and Technology
CRADA	Cooperative Research and Development Agreement
CRP	C-reactive protein
CSD	Chemical Sciences Division
CSD	Chemical Sciences Division
CSTL	Chemical Science and Technology Laboratory
ctDNA	circulating tumor DNA
DARPA	Defense Advanced Research Projects Agency
DFT	density functional theory
DHS	Department of Homeland Security
DMP	data management plan

DNA	deoxyribonucleic acid
DOC	Department of Commerce
DOD	Department of Defense
DOE	Department of Energy
DOJ	Department of Justice
DOT	Department of Transportation
EDRN	Early Detection Research Network
EGFR	epidermal growth factor receptor
ENP	engineered nanoparticle
EPA	Environmental Protection Agency
ERCC	External RNA Controls Consortium
ERF	equivalent number of reference fluorophores
FACT	Facility for Adsorbent Characterization and Testing
FBI	Federal Bureau of Investigation
FDA	Food and Drug Administration
FIB SEM	focused ion beam scanning electron microscope
FISH	fluorescence in situ hybridization
FIZ	Fachinformationszentrum Karlsruhe
FTE	full-time equivalent
GHS	Globally Harmonized System
GIAB	Genome in a Bottle Consortium
GM	General Motors
HER2	human epidermal growth factor receptor 2
HML	Hollings Marine Laboratory
HMP	Human Microbiome Project
IBBR	Institute for Bioscience and Biotechnology Research
ICSD	Inorganic Crystal Structure Database
IFCC	International Federation of Clinical Chemistry and Laboratory Medicine
IgG	immunoglobulin G
IMMSA	International Metagenomics and Microbiome Standards Alliance
InChI	International Chemical Identifier
ISO	International Organization for Standardization
IT	information technology
ITL	Information Technology Laboratory
IUPAC	International Union of Pure and Applied Chemistry
JANAF	Joint Army Navy Airforce
JILA	Joint Institute for Laboratory Astrophysics
JIMB	Joint Initiative for Metrology in Biology
LC-MS	liquid chromatography-mass spectrometry
LIMS	Laboratory Information Management System
Li-ions	Lithium-ions
low-GWP	low-global warming potential
mAb	monoclonal antibody

MATES	Multi-Agency Tissue Engineering Science
MCL	Molecular Characterization Laboratory
MDCS	Materials Data Curation System
MEP	Manufacturing Extension Partnership
MGI	Materials Genome Initiative
MIDAS	Management of Institutional Data Assets
miRNA	microRNA
MIT	Massachusetts Institute of Technology
MML	Material Measurement Laboratory
MMSD	Materials Measurement Science Division
MOU	Memorandum of Understanding
MSED	Materials Science and Engineering Division
MSEL	Materials Science and Engineering Laboratory
MTA	Materials Transfer Agreement
NCI	National Cancer Institute
NCI-MATCH	National Cancer Institute, Molecular Analysis for Therapy Choice
NCMC	National Cell Manufacturing Consortium
NDA	nondisclosure agreement
NDP	neutron depth profiling
NERSC	National Energy Research Scientific Computing Center
NGS	next-generation sequencing
NIAID	National Institute of Allergy and Infectious Diseases
NIDCR	National Institute of Dental and Craniofacial Research
NIH	National Institutes of Health
NIIMBL	National Institute for Innovation in Manufacturing Biopharmaceuticals
NIST	National Institute of Standards and Technology
NMR	nuclear magnetic resonance
NNSA	National Nuclear Security Administration
NOAA	National Oceanic and Atmospheric Administration
NRC	National Research Council
NREL	National Renewable Energy Laboratory
NSLS-II	National Synchrotron Light Source II
N-STEP	NIST Science and Technology Entrepreneurship Program
OAR	Open Access to Research
ODI	Office of Data and Informatics
OISM	Office of Information Systems Management
ORM	Office of Reference Materials
OSTP	Office of Science and Technology Policy
PECASE	Presidential Early Career Award for Scientists and Engineers
PLOT-cryo	porous layer open tubular cryoadsorption
PML	Physical Measurement Laboratory
R&D	research and development
REFPROP	Reference Fluid Thermodynamic and Transport Properties Database
RM	reference method
RMP	reference measurement procedure
SAXS	small-angle X-ray scattering



SBSC	Synthetic Biology Standards Consortium
SCB	Standards Coordinating Body
SD	service development
SEM	scanning electron microscopy
SERI	strategic and emerging research initiatives
SMSD	Surface and Microanalysis Science Division
SPRi	surface plasmon resonance imaging
SRD	standard reference data
SRI	standard reference instrument
SRM	standard reference material
STEM	science, technology, engineering, and mathematics
STR	short tandem repeat
TE	tissue engineering
TEM	transmission electron microscopy
TERMIS-AM	Tissue Engineering and Regenerative Medicine International Society-Americas
TMS	The Minerals, Metals, and Materials Society
UV-Vis	ultraviolet–visible spectroscopy
UMD	University of Maryland
URL	uniform resource locator
U.S. TAG	U.S. Technical Advisory Group
WCF	working capital fund
XRD	X-ray diffraction